VOLUME 52 NUMBER 2 FEBRUARY 1959

PROCEEDINGS
of the
ROYAL SOCIETY OF MEDICINE

Published by
THE ROYAL SOCIETY OF MEDICINE, 1 WIMPOLE STREET, LONDON, W.1

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All correspondence to

THE HONORARY EDITORS, 1, WIMPOLE STREET, LONDON, W.1

(Tel.: LANgham 2070)

Distributing Agents:

H. K. LEWIS & CO. LTD., 136 GOWER STREET, LONDON, W.C.1

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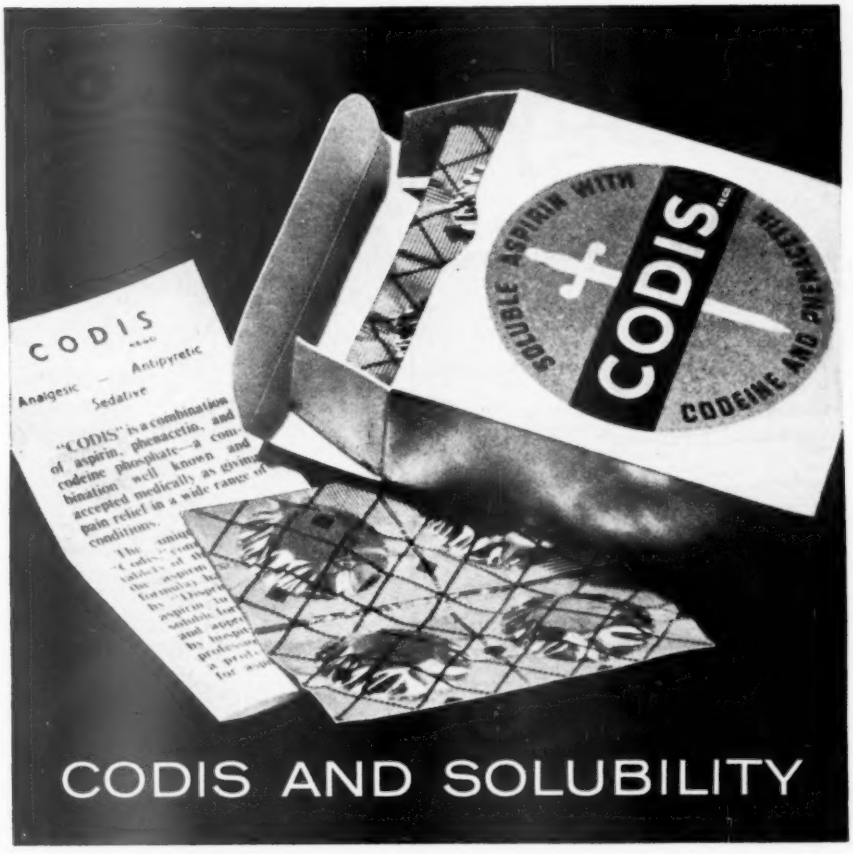

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REFERENCES
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Section of Proctology

President—HENRY R. THOMPSON, M.A., M.B., F.R.C.S.

Meeting
November 12, 1958

SYMPOSIUM ON RECTAL CONTINENCE

Mr. Denis Browne (London):

The heterogeneous group of deformities usually described as imperforate anus includes two quite distinct classes, those with an anal sphincter mechanism, and those which lack it. In the former normal continence can always be obtained, often by very simple means; in the latter it is doubtful if true control, of gas and fluid as well as solid fæces, is ever perfect. In the first class there is always, in my experience, a communication between the cavity of the bowel and the outer surface of the body; in the latter neither the anal sphincter mechanism nor the rectum has formed.

The term imperforate anus leads to a lot of misunderstanding and consequent bad treatment, and it would be a good thing if it could be dropped completely. I am aware, however, of the extreme difficulty of abolishing a misleading term, such as megacolon or undescended testicle, which has once become entrenched in the medical vocabulary. Another weakness in our terminology is the constant use of the word "fistula" to describe two very different conditions: a misplaced anus complete with sphincter mechanism, and also an abnormal communication between the bowel and another viscus, without any sphincter at all.

The classification which I would suggest is this:

Stenosis of the anus.—The abnormal narrowness of an anus which is obvious to view is surprisingly often overlooked in early infancy. Apart from the discomfort caused to the child, this condition is apt to set up a most obstinate and troublesome condition, which I call colonic inertia. In this the normal sensitivity of the rectum to the presence of fæces is lost owing to the constant pressure of large accumulations, and it is a difficult task to regain it, usually involving a long course of skilled washing out of the lower bowel.

Microscopic anus.—In this condition the communication between the bowel and the skin is so minute that it is only to be found on close examination. It is, of course, a variety of stenosis; but as it is not generally recognized and in consequence is often badly treated, I think it is worthy of a separate heading. It shows on the skin of the anal region as a minute blob of meconium, looking very like a "fly-speck". This is easily wiped away in cleaning the baby, and careful and repeated search may be necessary to find the opening.

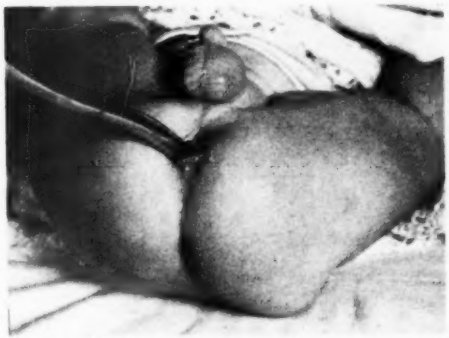

FIG. 1.—Dilatation of a microscopic anus, one month after surgical enlargement.

The treatment of both these types of stenosis is simple and satisfactory. The opening should be extended by a simple backward cut till it is of the normal size, and then this enlargement maintained by daily dilatations for several months (Fig. 1), till in addition to the healing of the raw surfaces all tendency to contract has been lost. This prolonged and persistent dilatation is of the utmost importance. Once the raw surfaces are healed the child does not object, and it is a powerful stimulant to the emptying of the lower bowel.

Ectopic anus.—The commonest type of this, the anus which has strayed forward into the lower part of the vagina (Fig. 2), is usually called by the dangerously misleading name of "imperforate anus with recto-vaginal fistula". This is apt to lead to the disastrous course of perforating the "imperforate anus" into the bowel at its normal site, and ignoring, or attempting to close, the "fistula".

Most of these ectopic anuses have greater or less degrees of stenosis, and the treatment of them is to get them to work normally as they lie, just as in the case of a stenotic anus in the normal position. In the female a minor degree of the condition may be called the "shot-gun perineum", the bowel and vagina opening side by side without

FIG. 2.—Vaginal ectopic anus of the type which will need transplanting to normal position.

FIG. 3.—"Shot-gun perineum" after dilatation. No further treatment necessary.

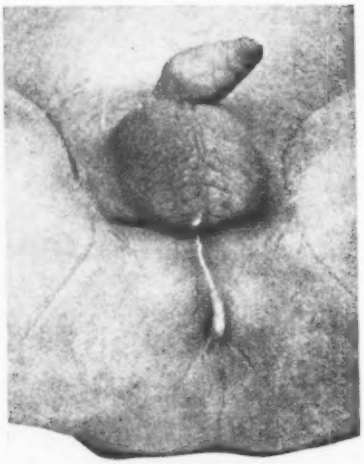

FIG. 4.—Covered anus, showing trail of white epidermal debris leading back to a normally functional sphincter.

the intervention of a perineum, like the barrels of a double shotgun (Fig. 3). When the anus is right inside the vagina it is of course most inconvenient, and should be transplanted to the normal position later in life, leaving an intact bridge of skin to form the perineum. This is a difficult and bloody operation, and should be postponed till 5 or 6 years of age. Personally I think it is as essential to divert the fæces during healing by a colostomy as it is to divert the urine when constructing a new urethra for hypospadias.

The male ectopic anus is uncommon, but needs nothing beyond the enlargement of the stenosis which is present in all cases I have seen.

Covered anus.—Everyone is familiar with cases, such as hare-lip, in which embryological processes of fusion have failed. It is possible that the converse process, that of excessive fusion, is responsible for an interesting group of deformities. In these there is in the normal situation a normal sphincter mechanism, but it appears to have been buried by an abnormal fusion of the genital swellings. In the male the only opening of the bowel is a minute tunnel leading forward for a greater or less distance, showing as a bluish or whitish line in the superficial layers of the skin, according as it is filled with meconium or detritus of the type found in a dermoid cyst (Fig. 4). Following this tunnel backwards leads to a functional anus, which is exposed freely and dilated in the same way as the stenotic types.

In the female the lower part of the vulva as well as the anus may be buried, and a very extensive incision is necessary to free them. An interesting variety is the covered anus associated with hypospadias, of which I have seen six examples. The anus is exposed first, and then the hypospadias treated by my buried strip method to give a perfect functional result.

Agenesis of the rectum.—In all the previously described varieties there has been a clue to the existence of an anal sphincter mechanism; in this extremely intractable condition there is none. In the male there is commonly a fistula into the prostatic urethra, showing its presence by a bluish stain of meconium in the urine. It is arguable whether the best treatment is a transverse colostomy or an immediate pull-through operation in which the blind end of the bowel is freed and brought out through a hole carefully stretched (not cut) in the floor of the pelvis. Two common measures are disastrous. The first is an iliac colostomy, which impedes access to the pelvis and ties down the bowel just where freedom is most necessary for a subsequent pull-through. The second is a blind dissection up through the minute pelvis, which wrecks the muscles upon which subsequent control must depend.

Tolerable control is occasionally obtained by the pull-through operation, but there is no space here for the analysis of the widely varying pathology and results.

Dr. L. Guttmann (Stoke Mandeville): *The Regulation of Rectal Function in Spinal Paraplegia*

Changes of intestinal activity, especially that of defæcation, as a result of afflictions of the spinal cord or spinal roots, have, for many years, been the subject of clinical and physiological

research. Among the outstanding studies made in this country during the last century, which have been fundamental in clarifying the intricate nervous mechanism of rectal function, may be mentioned those of Gowers (1899), Thompson (1899), Head and Riddoch (1917), Hurst (1921), Denny-Brown and Robertson (1935), and Learmonth and Rankin (1930).

Constipation is an early symptom of a spinal cord compression, and the improvement of a long-standing and stubborn constipation, following successful removal of an extramedullary or extradural tumour of the spinal cord, can be striking. The alteration of peristalsis and rectal function in spinal cord lesions has been attributed to the withdrawal of the control of cerebrospinal pathways, which, like those for the control of the bladder, descend within the anterior and anterolateral tracts of the cord. Foerster (1936) reported that bilateral cordotomy of these tracts resulted in paralysis of intestinal peristalsis, followed by marked meteorism. However, this paralysis was found to be transient, and normal intestinal activity returned within a few days. This has been accepted as proof that the central pathways, although exercising some correlating influence, are not essential for an efficient, reciprocal relationship between rectum and external sphincter. This relationship, which ensures a co-ordinated rectal evacuation, is controlled by the integrating function of the sacral segments of the cord and, in particular, the intramural autonomous innervation by the plexuses of Meissner and Auerbach.

This paper deals with observations made on the effects of complete and incomplete spinal cord lesions on rectal function in over 1,900 patients treated at Stoke Mandeville in nearly fifteen years. In more than 70% of the cases, the cord or cauda equina lesion was due to gunshot injury or fracture of the spine, involving levels from C.3 to S.5. The patients were admitted at intervals, following injury—some of them within the first few hours or days after injury. This enabled us to study their intestinal activities throughout all stages. Only features of special interest will be mentioned here.

The immediate effect of spinal cord transection on intestinal function was found to be a paralysis of peristalsis, especially in upper thoracic and cervical cord lesions, accompanied (in lesions at any level) by fæcal retention. On auscultation, the bowel sounds are either absent or scanty. Meteorism may develop fairly rapidly, but it was by no means a constant feature, and its degree varies, being, as a rule, absent altogether in lesions below T.10. However, it may become a dangerous complication in complete lesions of the mid-cervical cord, as it can interfere with the function of the diaphragm and thus increase the respiratory distress of the quadriplegic patient, which develops as a result of the paralysis of the intercostal muscles. Such a patient needs constant supervision by both medical and nursing staff, and the early intramuscular injection of 0·3 to 0·5 mg. of Prostigmin, combined with the introduction of a rectal tube, has proved beneficial and may become a life-saving measure. In a few cases, the paralysis of peristalsis also involved the stomach, and gastric suction became necessary to cope with its dilatation. The depression of gastro-intestinal function in the immediate stage following spinal cord transection, known as spinal shock, is a result of the sudden withdrawal of the central control. Consequently, the reflexes of micturition and reflex evacuation are abolished, and there is complete fæcal retention. Although, in due course, the automatic local function of the rectal wall and rectal sphincter recover, cases differ widely regarding the first spontaneous reflex evacuation and, in particular, the establishment of regular and efficient automatic evacuation.

There are many factors which influence the establishment and efficiency of rectal reflex evacuation, in the spinal man. Some may be summarized as follows:

(1) The pre-paraplegic motor, secretory and absorptive functions of the intestinal tract. Congenital anomalies, such as diverticulosis, enteroptosis or megacolon are as important as acquired habits of bowel evacuation at intervals of several days or even once a week, leading to chronic colonic stasis and dilatation. However, the majority of paraplegics or quadriplegics, without congenital or acquired anomalies in their pre-paraplegic gastro-intestinal life, do not as a rule exhibit abnormalities of upper gastro-intestinal motility in later stages following injury, as found in recent years in systematic X-ray studies of paraplegic patients by Keeler and Rusk (1952) and Dagradi (1953).

(2) The chemical and physical qualities of food affect their rate of passage through the intestinal tract. Foodstuffs of low residue (meat, rice, white bread, &c.) progress more slowly than those with high residue (cabbage, bananas, animal fat, &c.).

(3) The management of the patient in the initial, and later, stages of spinal paraplegia. We found that prolonged recumbency has an adverse effect on the establishment of early and efficient reflex defæcation. This was conspicuous in those paraplegics treated with prolonged recumbency in plaster beds, which was the method of treatment during the Second World War. Some of these patients were admitted not merely with overloaded rectum but with extreme

fæcal retention in all the large bowel. As a result, some of them were suffering from irritation diarrhœa. Moreover, the overdistension of rectum and colon may also have widespread reactions on autonomic mechanisms. These are similar to though less intensive, because of the plasticity of the colon, than those following distension of the bladder (Guttmann and Whitteridge, 1947). They consist of outbursts of sweating, pilo-erection and cardiovascular responses and are the result of reflex vasoconstriction in the paralysed part of the body, elicited by the intestinal distension. They are conspicuous in complete lesions of the upper thoracic and cervical cord, where the whole splanchnic outflow is situated below the level of the lesion and becomes involved in this reflex response. Certain subjective symptoms, such as feeling of heat, head fullness and headaches, particularly in the back of the head or between the eyes, may occur, as a result of the reflex responses of the vascular system. Practically, those concerned with the management of paraplegics must become familiar with this visceral distension syndrome, in order to relieve it and thus promote co-ordinated reflex evacuation of the bowels. We have found that regular turning of the patient in the early stages of paraplegia, early muscular exercise by the normal parts of the body and early restoration of the paraplegic's upright position, including standing and walking in parallel bars and on crutches, and the inclusion of sport in the physical rehabilitation of these patients, have proved beneficial in ensuring normal intestinal motility and co-ordinated reflex defæcation.

(4) The automatic reflex activity of the isolated cord below the level of the transection, which develops once the stage of spinal shock has subsided, may also exert its influence on reflex defæcation. This may occur particularly in lesions above T.7, in which the abdominal muscles are involved in the heightened reflex activity of the isolated cord, and spastic contractions of these muscles may interfere with the smooth passage of the intestinal contents through the intestinal tract, resulting in constipation. On the other hand, the momentary increase of abdominal pressure, as the result of prolonged spastic contraction of the muscular abdominal wall, in paraplegics with increased spasticity, may lead to sudden relaxation of the rectal sphincter, with consequent rectal incontinence. This type of incontinence differs from that seen in spinal cord lesions involving the conus and cauda equina, when, as a result of the transection of all the segments or spinal roots of S.2 to S.5, the anal sphincter and levator ani, as well as other perineal muscles, are flaccid and the sphincter becomes patulous.

Complete rehabilitation of paraplegic patients and their full re-integration into society is possible only if all the factors of their intestinal pathophysiology are understood and taken into account, when training these patients to regulate their bowels. It is emphasized that a regime ensuring regular and efficient bowel action once every twenty-four hours is as much an individual matter in the spinal man as in the normal person. During the stage of spinal shock, enemas may be necessary. However, as this passes, the establishment of a conditioned reflex defæcation at a regular time each day should be instituted—preferably after a meal, when the gastro-colic reflex can be utilized as an initiator of reflex defæcation. In order to facilitate such regularity, it is important to keep the contents in such a condition that the stool reaches the rectum firm but soft, and this is done by appropriate diet, mild laxatives or glycerin suppositories. Most important, the patient must be trained to use certain stimuli to elicit defæcation—as by digital dilatation of the anal sphincter or by cutaneous stimuli of so-called trigger zones in the sacral area (with or without massage or gentle rubbing of the abdomen or change of respiratory rhythm to increase the intra-rectal pressure)—the stimulus varies from case to case. Although, in a few enemas may occasionally be necessary, or, in others, digital evacuation, from our experience we would say that a satisfactory bowel regime can be achieved in the spinal man, wherever the lesion. The unphysiological approach of a few surgeons in treating the paralysed bowels of traumatic paraplegics by colostomy has fortunately never been accepted, and in the light of modern rehabilitation of traumatic spinal paraplegia, this method is hardly used.

In our experience, the re-education of the bowels following complete or severe lesions of the spinal cord or spinal roots has proved to be much easier than that of the bladder. This is one of the reasons why, to-day, so many paraplegics are able to participate in many social activities and to take up work held in competition with normal persons.

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Mr. C. M. Gwillim (London): *The Technique of the Repair of Old Complete Perineal Tears*

Thirty years ago the repair of old complete perineal tears was done in a rough way—in some cases with a Reverdin needle. The importance of sutures not penetrating the rectal mucosa was stressed. The only sphincter referred to was the superficial external sphincter. The results were often surprisingly good.

Figs. 1–6 (drawn by Mr. R. N. Lane) illustrate the repair operation.

FIG. 1.—The lines of the incision.

FIG. 2.—The separation of the vaginal wall from the rectal wall.

FIG. 3.—Further dissection showing the levator ani attached to the deep external sphincter, the superficial external sphincter, the conjoint longitudinal muscle and internal sphincter and the mucosa being united with closely approximated interrupted fine catgut.

FIG. 4.—Suture of conjoint muscle and internal sphincter with continuous catgut.

FIG. 5.—Suturing of deep external sphincter and superficial external sphincter.

FIG. 6.—Suture of levator ani.

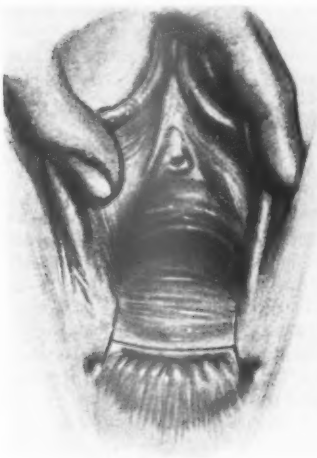


FIG. 1.

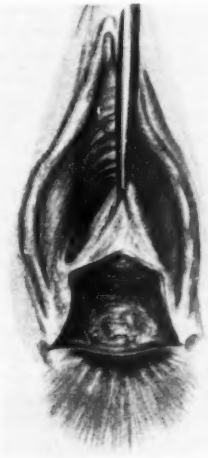


FIG. 2.

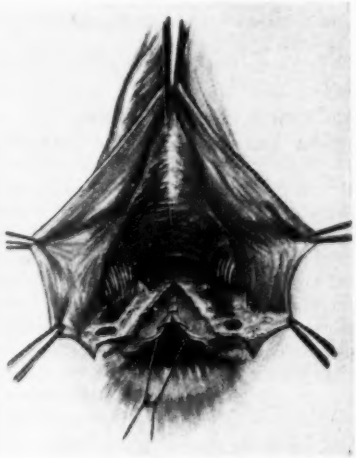
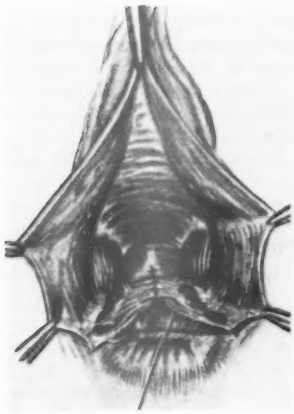


FIG. 3.



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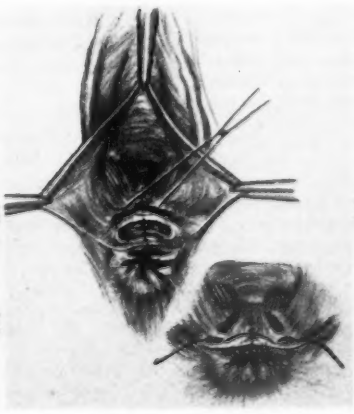

FIG. 5.

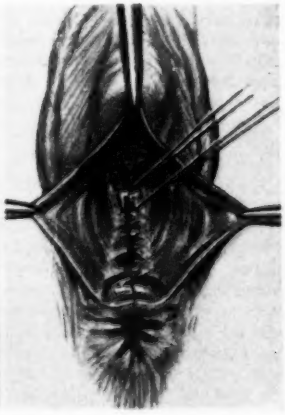

FIG. 6.

The operation is done slowly and meticulously. This reflects a general change in attitude and is partly due to the rarity of these cases, which is due to improved midwifery, the increased use of episiotomy and to the good results of immediate suture after labour.

The anatomy shown reflects the influence of papers by Milligan and Morgan (1934), Milligan *et al.* (1937), and Milligan (1943), reinforced by a paper in 1956 by Morgan and Thompson. They emphasized the importance of the internal sphincter and conjoint longitudinal muscle and of the deep external sphincter and the attachment of the levator ani into it at the ano-rectal ring.

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Mr. Charles Heanley (London):

Plastic and Reconstructive Surgery for Anal Incontinence

There are two types of anal incontinence of interest to the plastic surgeon. First, where there is loss of perineal skin and tissue anterior to the anal canal due to surgery or obstetrical mishap, skin cover can be provided by two rotation flaps based posteriorly and rotated inwards. This can be done either after muscle reconstruction or before a gracilis muscle transplant. The second type is where there is loss of epithelium resulting in a stricture which may also be associated with loss of muscle tissue. The following case is an example:

After penicillin for a chest infection a woman developed severe loss of anal tissue. When I first saw her a colostomy had been performed and the anal canal was strictured with loss of muscle. The anus was considered as a tube around which is wrapped muscle. The right gracilis tendon was detached from the tibia through a small incision. The muscle was then freed in the thigh through a four-inch longitudinal incision as high up as the entry of artery and nerve. Two incisions were made on either side of the anus and by blunt dissection a pathway was made from the thigh through the attachment of Scarpa's fascia and round the anal canal keeping well above the level of the perineum. The gracilis tendon was threaded through this gap pulling behind it the muscle wrapping the gracilis from the right clockwise, in front of, behind and again in front of the anal canal to suture the tendon with braided nylon to the fascia of the left tuber ischii. Some three weeks later the stricture was divided by a longitudinal incision; this results in a diamond-shaped raw area and into this a flap was transposed from the buttock to form the new anal canal, the donor site of the flap being grafted.

No post-operative dilatations are required. I would regard post-operative dilatation as failure of a stricture operation. Subsequently the colostomy was closed. The post-operative result was satisfactory inasmuch as she could pass stool and control solids.

In some other cases I have had trouble from sepsis and feel they are best treated post-operatively by constipation rather than antiseptics which may result in diarrhœa.

Professor J. Chassar Moir (Oxford):

Many doctors look upon an obstetric injury of the perineum as a triviality. Vaginal tearings, lacerations of the pelvic floor, rupture of the anal sphincter, even splitting of the anal canal, are often regarded as the inevitable consequences of childbirth calling, perhaps, for a couple of deep sutures and a stitch in the skin of the perineum. It is a tribute to the adaptability of the human pelvic structures that such a repair is sometimes effective in restoring a more or less normal function to the organs concerned.

But every gynæcologist knows that such a fortunate result is far from being the rule. Nearly half my time as a gynæcologist is taken up with attempts to make good the damage caused, directly or indirectly, by obstetrical injury, much of which should never have occurred or, having occurred, could have been rectified at the time by precise repair. I am not an opponent of the general practitioner who engages in obstetrics, but I know that there can be few practitioners who are competent, without special postgraduate training, to detect, and to treat adequately, the more serious perineal injury which can occur unexpectedly and which, if untreated, can condemn the woman to lifelong rectal incontinence.

I repeat that while there is much to be said for domiciliary midwifery, I for one should be happier if I knew that every midwife had the discernment and initiative to make an episiotomy when that prophylactic operation was indicated; and that every doctor had the skill to suture a deep perineal tear so that the pelvic floor and its components are restored to their pre-partum state. The following cases are examples:

Case I.—A young married woman having her first baby had a spontaneous delivery complicated by a perineal tear for which the doctor had been summoned. The tear was repaired; but, as there was a continued loss of dark blood, the patient was sent to hospital a week later with the diagnosis of a retained portion of placenta.

Examination under anæsthesia failed to show any placenta, but there was a severe perineal laceration which was united by skin only. When this skin bridge was snipped it was evident that the whole of the deeper structures of the perineum had been ruptured. The ends of the torn anal sphincter had retracted widely and the anal canal was completely

split and lying wide open. There was no evidence that these structures had been sutured; and it can only be supposed that in the conditions in which the doctor had made his examination he had failed to realize the extent of the injury. With careful stitching of the anal canal and of the external sphincter, this patient made an entirely satisfactory recovery.

Case II.—A woman had a large vesico-vaginal and recto-vaginal fistula caused by radium treatment some years previously for carcinoma of the cervix. An inguinal colostomy had been performed and, as repair of the fistulæ was out of the question, a high colpocleisis was effected. The result of this was to divert the urine from the damaged bladder into the rectum, where it was retained by the anal sphincter. This operation was at first satisfactory but shortly the patient found that she had a leakage of urine from the anus especially during sleep. A closer examination showed that the anal sphincter, which had previously been regarded as adequate, was defective. There was a misleadingly good perineum, but a thin scar indicated an old obstetric injury. A dissection made the local defect clear. The anterior half of the anal canal was devoid of any sphincter; the ends of that muscle had retracted out on both sides leaving only thin scar tissue which merged with the apparently normal perineum.

Here was another example of a failure to repair, layer by layer, and structure by structure, the anatomical components of the pelvic floor.

My contribution to this discussion is to proclaim the common cause of anal sphincteric defect in parous woman. *It is*, in my opinion, *the failure of the medical attendant to appreciate the nature of the injury at the patient's delivery.*

Regarding the immediate repair of a third-degree perineal tear, the essentials are a good anæsthetic, a good exposure of the parts, a good spot-light, patience and care by the surgeon.

I think of only two anal sphincters: one (the internal sphincter) can be regarded as part of the muscle wall of the rectum and the anus; the other is the external sphincter which is an obvious structure, nearly as thick as one's little finger.

The muscle wall of the rectum and anus is sutured with a running catgut suture so placed that the mucosa is turned inwards. The external sphincter is almost always torn to one or other side of the mid-line with the shorter portion deeply retracted. This portion must be identified and raised out of its pit with Allis' forceps. The ends of the sphincter are united with two or possibly three interrupted catgut sutures. The remainder of the repair is as for any other perineal rupture.

There are one or two points to add. The catgut stitching should be adequate, but not over-generous, for too much foreign body will cause sepsis and non-union of the parts. The catgut should be as thin as is consistent with the mechanical purpose in hand. I use B.P.C. No. 0 for the purposes mentioned, with 2/0 for the over-and-over stitch which brings together the structures of the perineum itself.

The repair of a third-degree tear is sometimes marred by a small fistula developing at a high level between the rectum and the vagina. This can be avoided by deliberately separating the vaginal wall from the rectum for 2 cm. above the level of the anal or rectal tear. This is easily accomplished; and the stitching first of the rectal wall, and then of the vagina, can be made with accuracy and ease.

Regarding after-treatment, the patient should be put on half-ounce doses of liquid paraffin twice daily from the first day, and the paraffin continued in decreasing doses for three or four weeks. This treatment ensures easy defæcation—even a seepage—around the fourth or fifth day. The opposite treatment is advised by some authorities—namely to keep the bowels confined and to administer an enema on the sixth or seventh day. I have never been able to understand this. Even if the patient can remain constipated to order—which is not always the case—it seems preposterous for her to expel something akin to a cannon ball at the time when the catgut stitches are being absorbed and before the union has had time to consolidate.

The repair of a sphincter, or of a torn anal canal plus a torn sphincter, is not a particularly difficult operation although it does require care. I have never had an anatomical breakdown or a functional failure; and this applies also to secondary-suture cases which have been sent to hospital after failure of primary repair.

This statement raises a question: when should re-suture be attempted after a previous breakdown? The answer is most certainly *not* after a delay of six months. I prefer to make the re-suture as soon as the surfaces look reasonably clean—usually three or four weeks after the initial attempt.

I take every opportunity of impressing on my students that the repair of a third-degree perineal tear is not a particularly urgent operation. If the home surroundings are unsuitable for surgery it is better to postpone the operation and to transfer the patient within the next twelve or twenty-four hours to a hospital or nursing home where the repair can be accomplished in surroundings where assistance, efficient light and appropriate instruments are at hand.

Mr. Ian P. Todd (London):

Normal complete rectal continence is a remarkable asset. Most of us achieve this in early infancy. Exactly why most children learn bowel continence easily is difficult to understand, as maternal training seldom amounts to much.

Bowel habit, that is regular emptying, is a different problem, and I believe vigorous training can occasionally help. In the difficult case, one must be sure that there is no organic cause for the failure.

Complete continence implies control of, and differentiation of, solids, liquids and gases. Often one of these functions is incomplete, particularly after anorectal operations; it is discovered only by direct and uninhibited questioning about each function. Continence implies a normal receptor area, uninterrupted nerve pathways connecting this to the conscious or subconscious mind, and a motor component which is able voluntarily to refuse or augment the defæcation impulse. To this is added an involuntary mechanism, which can, on occasions, cause fæces to be expelled automatically or reflexly unless voluntary inhibition or other obstruction prevents it.

In the normal control of solid fæces the everyday receptor mechanism is within the lower 5–7 cm. of the rectum. If this area is not present (either because it has never existed, as in rectal agenesis, or because it has been removed, as in some pull-through operations) normal continence is not possible. Neither colon nor grafted skin can take the place of this section of rectum. Luckily there is a subsidiary mechanism of continence within the sphincteric canal which is more commonly concerned with differentiation and voluntary control of liquid fæces or flatus. It is this area which is the saving grace of surgeons and gives them those few cases of adequate though abnormal continence which follow some pull-through operations.

The internal involuntary sphincter ani is the usual mechanism of maintaining continence unconsciously. As the rectum fills, tone in this muscle falls, but before relaxation is complete and at a given volume of rectal distension, a sensory impulse—the call to stool—is evoked. There is a rectal contraction which occurs when passive distension of the rectum has reached a definite volume and it is this, as in the bladder, that causes the sensory call.

The sensory impulse is either answered and the bowel emptied, or it is refused. It is now that the normally tonic voluntary external sphincter ani muscle is called into play, but it can only be contracted forcefully for 50–60 seconds before it tires. During this time "passive adaptation"—really a kind of relaxation of the rectal wall and lowering of intrarectal pressure—occurs in the rectum. Thus the internal sphincter can recover some of its tone and involuntary continence once more be regained.

Fluid and flatus can easily slip past the lower rectal sensory area, in which stretch appears to be the activating stimulus, without irritating it. They impinge upon the sensitive papillæ within the sphincteric mechanism and excite a peripheral sensory response.

The variability of the site of change of epithelium in this area has been pointed out by Walls (1958, *Proceedings*, **51**, 425). It may be that the peripheral nerve supply is carried upwards with the squamous epithelium, and some of the odd sensory responses, for example the painful needle prick and reaction to hæmorrhoid-injection, could be explained in this way.

Gas and diarrhœa normally can be controlled because the internal sphincter is somewhat tonic and the external sphincter can be rapidly brought into play voluntarily. With a full rectum and a relaxed internal sphincter, control is more difficult. Complete internal sphincter section in one plane, the external sphincter being intact, causes incomplete control, in which leakage occurs before the voluntary response can be evoked. Removal of the rectal sensitive area has an effect on continence similar to that of cutting the internal sphincter. The reason for this is obvious, as the internal sphincter loses its "sensory" apparatus. However, the effect here is permanent, whereas it is transitory when the muscle is transected, for in three to four days it will heal, the external sphincter splinting its repair.

Sphincteric control is partly involuntary, when it concerns the internal sphincter, the sensory area being the lower rectum, and partly voluntary, when it concerns the external sphincter, the local sensory area being the papillary region. The external sphincter can be voluntarily contracted at any time, but this cannot be maintained.

The patulous anus can be a difficult finding to interpret. It is most marked in some neurological conditions and a cauda equina lesion, where the reflex arc is interrupted, probably exhibits the most profound changes. It is of interest that this is the only lesion known to cause complete rectal prolapse in both man and animals.

Chronic constipation begins as a vicious circle. A distended rectum causes internal sphincter relaxation; with voluntary external sphincter contraction and refusal of the call to stool, plastic adaptation of the rectum occurs. If the next call to stool is refused, rectal over-distension causes persisting relaxation of the sphincter and normal tonus is finally impaired. Internal sphincter tonus cannot be regained voluntarily. Sphincteroplasty operations must either aim to get muscle fibres contracted down to their normal length—thus operations of the Thiersch type—or make use of a new muscle and condition a voluntary reflex to answer the sensory call in a new way—that is gracilis transplants and so on. The trouble with the latter operation is that the

answer is often apt to be a little late as the only sensory stimulus may be delivered half-way out of the sphincteric canal. Plication sphincteroplasties are useless as they try to make use of already overstretched muscle fibres. External sphincter tone can be regained by voluntary exercises, but the speed of reaction to the sensory stimulus is perhaps as important as the muscle tone.

Normal continence depends, therefore, on a normal rectal sensory area and a normal papillary sensory area. The former is concerned with internal sphincter response, the latter with part of external sphincter response. The two together account for normal anal sphincteric tone. Loss of both sensory areas, either surgical, idiopathic or neurological, will cause incontinence just as division of both muscles will cause it. Loss of either sensory area, surgical, idiopathic or neurological, will probably lead to urgency and soiling just as division of one or other muscle will do. Thus, though it is unwise surgically to jeopardize normal continence if it can be avoided, one can fairly safely predict the end-results of most operations. I do not believe in a rectal "proprioceptive" mechanism, where fine touch gives rise to the sensation of wind. Neither do I believe that a weight of fæces in the pelvis or perineum is a useful sensory stimulus; at least experimentally it does not seem to be so. I cannot believe in levator control and I believe the levator diaphragm is essentially a defæcatory and respiratory muscle. Perhaps others will disagree here but voluntary contraction cannot be prolonged, and it is certainly a conscious act. Rectal continence is not. We must, however, remember in pull-through procedures that the colon, though unable to produce a call to stool and notoriously willing to undergo plastic adaptation, can be conditioned to empty, and perhaps extraneous sensory stimuli may reinforce this conditioned reflex and pseudo-continence.

Finally I would like to suggest that there are conditions in which rectal sensory loss is primary and the resulting constipation does not respond simply to medicine or surgery. If involuntary continence is over-zealous, therefore, one should look for abnormalities in its physiology.

Professor J. C. Goligher (Leeds):

My part in this symposium is to recall the functional imperfections of various forms of sphincter-saving resection for carcinoma of the rectum and rectal prolapse. Unfortunately, though these operations preserve the sphincters, they do not always preserve rectal sensation, which, as Mr. Todd has emphasized, is such an important component of the mechanism of continence, and for this and other reasons impairment of anal control sometimes results.

The most destructive sphincter-saving resection is the pull-through abdomino-anal excision of Bacon (1945) and Babcock (1932, 1940, 1947) which is popular in America though not in this country. In the *Bacon version* of this operation the actual pull-through is achieved by "coring" out the anal mucosa as a circular cuff from just below the pectinate line to just above the sphincters. The plane of separation is then deepened through the muscular coat of the rectum into the pelvic cavity. This frees the previously mobilized rectum which can then be drawn through the anus till the upper sigmoid is lying in the anal canal and a stump of colon projects 7 to 8 cm. beyond the anus. Some two weeks later after union has taken place the excess colon is trimmed off with diathermy flush with the anal orifice leaving the anal canal lined by colon wall.

This technique removes all the sensitive ano-rectal mucosa and on theoretical grounds it could not fail to render the patient incontinent. For that reason I was never attracted to it, till I was in America a few years ago and saw Dr. John Waugh of the Mayo Clinic performing it, and talked to him about his results. He admitted that the majority of his patients did not have proper continence after it, but thought that about a third of them had normal anal function. Stimulated by this I resolved to give the operation a trial and on my return did 7 such cases in succession. I have no doubt from my interrogation and examination of these patients after operation that they were all devoid of true rectal sensation and incontinent. They had merely perineal colostomies and would have been better off with abdominal colostomies.

In the *Babcock version* of the abdomino-anal pull-through operation, the small ano-rectal stump is left with its mucosa so that union can only take place between the cut upper end of the stump and the serosal aspect of the colon. This might be expected to preserve rectal sensation and ensure adequate control, but Babcock divides the sphincters to avoid undue compression and necrosis of the colon stump, and its subsequent retraction into the pelvic cavity before union had taken place. Marden Black of the Mayo Clinic uses the Babcock operation but without division of the sphincters and has apparently had satisfactory results and good anal function. I was less fortunate in the two cases I treated by this method; one of them did develop colon stump retraction and subsequently died on that account. Altogether I think this is a dangerous operation.

Another form of abdomino-anal resection with which several of us are familiar in England is the *Maunsell-Weir type of operation*, which we

ought perhaps to call the Lloyd-Davies method, for he developed it without knowledge of its prior description. The general plan of this type of abdomino-anal resection is to resect the carcinomatous segment of bowel through the abdomen, leaving a long colon stump and a short ano-rectal stump. The latter is then turned inside out through the anus and the colon stump drawn down through the everted anal canal. The cut edges of both stumps can then be sutured together outside the anus, as a tailor sews a sleeve into the everted body of a jacket. Finally the anastomosis is pushed back into the pelvis through the anus. By this means it is possible to achieve a very low colo-rectal anastomosis without division of the sphincters, and without sacrifice of the anal or lower rectal mucosa. Satisfactory anal continence might therefore be anticipated in most of these cases, and this is in fact achieved, though in a number of the 24 patients I have examined after this type of resection, control for flatus and liquid fæces was impaired for several months after operation, and this, together with frequent motions, proved a considerable inconvenience. Most of these patients became fully continent eventually, but 5 or 6 continued to suffer from some degree of incontinence. I would emphasize the long period of rehabilitation of bowel function necessary after this operation and also the relatively high complication rate due to necrosis of the colon stump, separation of the anastomosis, &c.

Anterior resection is the only really satisfactory form of sphincter-saving excision for cancer. With this operation, even when performed as low as is technically feasible, a substantial rectal stump is left, usually representing at least the lower third of the rectum. It would seem that this ought to ensure adequate sensation post-operatively and, as the sphincters themselves are completely untouched, it would be reasonable to expect normal continence after this operation. The only way in which anterior resection might theoretically interfere with the mechanism of continence is by denervating the ano-rectal stump of its parasympathetic and afferent nerve supply, if it were too extensively mobilized. In actual practice, however, despite the fact that the rectum has frequently been freed right down to the ano-rectal ring, no impairment of continence seems to result. In a careful enquiry comprising over 100 patients treated by low anterior resection I found that in only 2 elderly and rather apathetic individuals was there any complaint of incontinence. Yet they both appeared to have adequate rectal sensation on balloon distension and their sphincters exhibited normal tone and contractibility. I felt inclined to attribute the lack of control in these 2 patients to senility and general indifference. In the other patients anal control was perfect though for three to six months the motions were more frequent than normal.

Rectosigmoidectomy for rectal prolapse has a notorious reputation for incontinence, and this has been attributed by Hughes (1949), Goligher (1951), and others mainly to impairment of rectal sensation by removal of too much of the ano-rectal mucosa. In performing recto-sigmoidectomy nowadays most surgeons make a point of retaining at least 2·5 cm. of anal mucosa above the pectinate line in the anal stump. I cannot say whether this modification of technique makes much difference to the functional results for I no longer use this operation. But I am quite sure it is not the whole story and that the poor state of the sphincters, and possibly other factors, play a part in the causation of incontinence in these cases. In other words, control is often poor before operation, but this fact is obscured by the prolapsing of the rectum. I am struck by the fact that after other operations for this condition which do not resect bowel—or at least not the important lower third of the rectum—the functional results are also often unsatisfactory. Thus after 32 Roscoe Graham repairs and 4 anterior resections by me for rectal prolapse, rectal function was good in only about half the cases. In another quarter the patients seemed to spend a lot of time having frequent, small, pellet-like motions, and, if they tried to ease matters with larger doses of aperients, were liable to have accidents. The remaining quarter were even more incontinent and had to wear perineal pads constantly. With either of these two operations I am now daring enough to believe that I can cure most cases of complete rectal prolapse in an anatomical sense, which was not possible with recto-sigmoidectomy with its 50% recurrence rate, but I must confess I am far from happy about the quality of the functional results, which I regard as being not much better than those obtained with the latter operation.

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Proceedings of the Royal Society of Medicine

Vol. 52
95

Section of Anæsthetics

President—H. J. V. MORTON, M.D.

Meeting
November 7, 1958

Pharmacological Testing of Anæsthetics

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THE pharmacological investigation of new anæsthetics raises problems which certainly require discussion. It is, however, a matter of satisfaction to point out that the need for pharmacological investigation is now universally accepted, and that no one to-day would propose to make the first tests of anæsthetic potency directly on man. This change of attitude is fairly recent, for I understand that when trichlorethylene was introduced, very little pharmacological evidence was accumulated.

The interest in new anæsthetics to-day has developed out of the concern of the Ministry of Health to diminish the risk of explosions in the operating theatre. It is not so much that explosions often occur, as that considerable sums must be spent to minimize the risk of their occurrence. This has directed attention to the discovery of a non-explosive anæsthetic with the idea that if one was discovered which was in every way suitable, then it would be possible to banish substances like ether and cyclopropane from general use or at least from use in the National Health Service. Ether, however, although highly inflammable is an anæsthetic which an untrained person can use, and if a new anæsthetic was to replace ether, the anæsthetic would have to be not only non-explosive, but equally safe. This is a very severe requirement.

It is against this background that the Pharmaceutical Division of I.C.I. introduced halothane. They knew that hydrocarbons became less inflammable when fluorine was introduced into the molecule, and they tested a series of compounds containing fluorine, and found that halothane was a satisfactory anæsthetic. According to his description of the pharmacological work, Raventós (1956) began by testing on mice.

Tests on mice.—We have had some experience at Oxford in carrying out tests on mice. Mr. P. J. Goodford has made the experiments under the supervision of Dr. H. G. Epstein. We have used an apparatus almost identical with that described by Raventós, and found it quite satisfactory. The problem is not merely to find out whether the substance under investigation will anæsthetize mice, but to determine what anæsthetic action is possessed by different concentrations of the substance. Raventós's apparatus was arranged to deliver a known amount of anæsthetic per minute into a warm chamber where it met a current of air flowing at a known rate per minute. In the chamber the anæsthetic was vaporized, and thus a current of air containing a known percentage of anæsthetic was obtained. The current passed into another larger chamber in which a group of 10 or 15 mice were placed. The effect on the mice was determined during a period which might be 15 or might be 60 minutes. The proportion of mice was observed which were sufficiently anæsthetized (*a*) to be unable to right themselves, and (*b*) to be unaffected by a pinch applied at the base of the tail. After exposure to the anæsthetic the mice were taken from the chamber and observed during the following two weeks to see if any of them died.

Mice are extremely useful for testing anæsthetics and much information is gained from them. Whereas many drugs vary in their action in different animals, this is not true of anæsthetics. Morphine is well known to have a sedative effect in a dog, but to excite a cat. No such difference is observed in anæsthetics. Both the inhalation anæsthetics and the injection anæsthetics have the same action in all species, and in many species the anæsthetic concentration is the same. Thus the range of anæsthetic concentration of ether is 6 to 8% ($^{v}/_{v}$) for mice, as it is for dogs and for men. I do not wish to suggest that ether is anæsthetic in this concentration for all species, for I am reasonably sure that this concentration would not anæsthetize a goat.

Using Raventós's apparatus, we found it possible to compare different anæsthetics in different concentrations.

Table I shows the results of comparing two anæsthetics, A and B, with ether and with halothane, the tests being of fifteen minutes' duration. Each figure shows the result in a group of 10 mice. Thus ether in 4% concentration anæsthetized 6 out of 10 mice, and in 6%

concentration it anæsthetized 10 out of 10. When ether was applied in 10% concentration, one mouse subsequently died, and when applied in 14% concentration, all mice died. These comparisons were then summarized by calculating for each anæsthetic the concentration which anæsthetized 50% of mice, and also the concentration which killed 50% of mice. The ratio of these figures provided a therapeutic index which measured the safety of the anæsthetic. The results are given in Table II and show that compounds A and B were less safe than either ether or halothane. These were similar in degree of safety. The LD50 for ether, that is the concentration of ether which caused death of half the animals, was much higher than the figure given by Raventós. This is probably because Goodford injected atropine beforehand, so that higher concentrations of ether were tolerated better.

Tables I and II illustrate the way in which anæsthetics can be compared in groups of mice and an estimate of their relative safety can be obtained. In Table I the period of anæsthesia was for fifteen minutes only, and more information is gained when longer periods are used. Thus Goodford found that neither 7% ether nor 2% halothane caused any deaths when the mice were anæsthetized for fifteen minutes, but as the time of exposure was lengthened up to sixty minutes, more and more mice under 7% ether died, while under 2% halothane there were no deaths. The two compounds A and B each had a low therapeutic index; this by itself indicated that they were inferior to ether and to halothane, but in addition Goodford observed that both these compounds caused initial excitement and also convulsions during anæsthesia. Thus they were unsuitable as anæsthetics on other grounds than the therapeutic index.

TABLE I.—RESULTS AFTER FIFTEEN MINUTES
Column A is number of mice anæsthetized out of 10
Column D is number of mice killed out of 10

% v/v Conc.	Compd. A		Compd. B		Ether		Halothane	
	A	D	A	D	A	D	A	D
0·85							1	0
1·0	9	0					4	0
1·25							9	0
1·5	10	2					10	0
2·0	10	9					10	0
2·5							10	0
3·0					0		10	3
3·85							10	4
4·0					6		10	3
5·0			1	0			10	10
6·0			9	0	10			
7·0					10			
8·0			15*	0	10			
9·0								
10·0			10	0	10	1		
11·0			10	2				
12·0			10	7	10	5		
14·0					10	10		

*Out of 15 mice.

TABLE II.—ANÆSTHETIC AND TOXIC DOSES AFTER FIFTEEN MINUTES

Compound	AD_{50} % v/v Conc.	LD_{50} % v/v Conc.	$\frac{LD_{50}}{AD_{50}}$
A	0·8	1·7	2·1
B	5·5	11·5	2·1
Ether ..	3·8	11·8	3·1
Halothane ..	1·05	3·6	3·4

It will thus be clear that mice are very useful animals for testing anæsthetics and have the great advantage that they use little material. For one of the troubles about testing new anæsthetics is that the supply provided by the chemist is almost always very small. The chemist can provide a sample of 10 to 20 ml. without great difficulty, but a quantity of 200 ml. may take six months to prepare. Any programme of investigation will in fact run up against the obstacle that there is not enough material. If a thorough investigation on mice has shown that a new substance compares favourably with ether, the substance should then be taken straight to the dog for trial under the conditions of an ordinary surgical operation.

It is, of course, not everywhere that this is possible. However, at Oxford we are in close relation with the Nuffield Department of Anæsthetics and with the Nuffield Department of Surgery, and therefore we can have the services of a highly trained anæsthetist and of Professor P. R. Allison's first assistant, Mr. A. J. Gunning, as surgeon. Nor is this all, for we work with Dr. H. G. Epstein who ensures that proper methods are used to administer a precisely known concentration of the anæsthetic, and with Mr. O. B. Saxby, the mechanical engineer in the Department of Pharmacology, who makes whatever equipment is required. I daresay that there is no other place in the world, either inside or outside a university, where such favourable conditions exist.

This collaboration began when I was Chairman of the Committee for Non-explosive Anæsthetics appointed by the Medical Research Council, and when we first received a sample of what was later called halothane from I.C.I. At that point the supply of material though small was not minimal, and we carried out several experiments with dogs to observe for ourselves the effect on respiration, blood pressure and on the ECG. However, I felt very strongly that the final test

had not been made, the test that ought to be made before clinical trials were begun. No operations had been carried out on dogs to see how well they would tolerate operation under the new anæsthetic. Operations were therefore carried out by Mr. A. J. Gunning; among these there was one in which the chest was opened and the mitral valve was exposed. The anæsthetics were given by Dr. A. B. Bull, and on some occasions Sir Robert Macintosh came to watch. Before and after the operations the dogs were kept in metabolism cages so that the daily urine flow was measured and the general condition closely observed. The results were striking enough, for the dogs made an excellent recovery in all cases and looked fit and well on the following day. The urine flow remained normal.

I have suggested then that the first two steps to be taken in investigating a new anæsthetic are first to study its action by quantitative methods on mice, and if it appears satisfactory in these tests then, because the supply of material will certainly be small, to try it at once in operations on dogs.

A skilled anæsthetist learns at once whether induction is smooth, whether the substance causes difficulty in respiration, whether it stimulates secretion from mucous membranes and whether it gives muscular relaxation. He further learns if the dog makes a rapid recovery. If all these points are satisfactory it is then possible to tell the chemist that he must prepare a larger supply, since the outlook is bright.

The further examination of an anæsthetic concerns an analysis of, first, the immediate effects and, second, the late effects of its administration, and certain points relating to the immediate effects deserve consideration. Thus there is still no final agreement about the action of halothane on the cardiovascular system.

Causes of a hypotensive action.—It may be of interest to consider briefly the causes of a hypotensive action in the light of experience with halothane. The blood pressure is maintained by the combined action of the heart and blood vessels, and it is therefore clear that a fall of blood pressure may be caused by weakening of the heart or by loss of tone in the vessels.

The effect of an anæsthetic on the output of the heart can be accurately determined in the heart-lung preparation since the venous pressure and venous inflow are kept constant and the arterial pressure is also kept constant. Actually halothane was found to have a depressant action nearly as great as that of chloroform. However, in the body various compensatory mechanisms are at work and an agent which diminishes the output in the heart-lung preparation may not always diminish the output in man.

The blood vessel tone is governed by the stream of impulses from the vasomotor centre, and an anæsthetic may diminish vascular tone by diminishing these impulses. It is certain that ether increases these impulses (Bhatia and Burn, 1933) but some anæsthetics may diminish them. Thus the M.R.C. Committee's report on halothane (1957) suggested that the main cause of hypotension was a diminution of the outflow from the vasomotor centre.

The fall in blood pressure may be due to a ganglion-blocking action of the anæsthetic. This has been regarded by Raventós as the main cause of the fall of blood pressure due to halothane. However, the standard test for ganglion-blocking agents has always been the action on the superior cervical ganglion of the cat, and on this ganglion halothane has by itself very little effect. Raventós has therefore suggested a blocking action mainly exerted on mesenteric ganglia, but halothane still causes a profound fall of pressure in the eviscerated animal in which block of mesenteric ganglia can play no part. Moreover agents which selectively block some ganglia but not others have been sought with great diligence by many pharmaceutical firms, so far without success.

Finally a fall of blood pressure may be due to the direct action of the anæsthetic on the blood vessel walls. Dr. Epstein and I have recently observed that halothane has such an effect on the vessels of the dog's hindleg perfused with blood. The blood was oxygenated by pumping through the lungs, and halothane was administered by mixing it with the air used to inflate the lungs. Halothane in 1·5% concentration caused a fall in arterial resistance in the leg vessels from 170 to 132 mm. Hg in one trial, and from 153 to 119 mm. Hg in a second. This fall was accompanied by an increased venous outflow, and when halothane was stopped the arterial resistance once more rose. Ether in 6% concentration had no effect of this kind, and in 8% concentration caused a fall of a few millimetres only.

A new anæsthetic should also be tested to see if it makes the heart sensitive to the action of adrenaline when injected intravenously. It is well known that, under chloroform anæsthesia, adrenaline administered in this way may cause ventricular fibrillation, and both halothane and cyclopropane have a similar effect. It is important to make certain that a new anæsthetic has no excessive sensitizing action of this kind.

The foregoing observations thus briefly indicate how the action of an anæsthetic on the cardiovascular system can be analysed. Such an analysis obviously depends on the use of experimental methods in a pharmacological laboratory.

The late effects.—The late effects of the administration of an anæsthetic can be studied in small animals by making histological studies, and by various other methods. Compounds which are related to chloroform, however distantly, are naturally suspected of having a toxic action on the liver or on the kidney, and a thorough study is necessary to clear them of this suspicion.

Application to man.—When the pharmacological tests have given satisfactory results, there comes a point at which a new anæsthetic should be tested on man. Opinions differ about the stage at which clinical trials should begin, and these differences are of sufficient importance to deserve discussion.

My own view is that the essential features of the pre-clinical testing are two. One is that the anæsthetic should be used during full-scale surgical operations on dogs, and should be found to allow prompt and satisfactory recovery. The other is that the anæsthetic should be shown to be free from a toxic action on the liver, kidney and other organs.

But someone else may have a different view, insisting that the anæsthetic should not be tried in man until the details of the fate of the anæsthetic have been thoroughly determined. It might be suggested, with reference to halothane, for example, that atoms of fluorine may remain in the body, causing pathological changes after a period of two or three years, and that we cannot yet be sure whether the use of halothane will not have serious consequences long after its administration. This is an extreme view, which can be held only by very few if we consider the widespread use which halothane has already achieved.

When we reflect on the large number of important new remedies which have been introduced as a result of tests in animals and which have been shown to have a similar action in man, it seems to me difficult to give any consideration to the idea that a new anæsthetic which behaves satisfactorily in mice and in dogs may conceivably be dangerous for man. Almost all the specific remedies right back to diphtheria antitoxin have been worked out on animals, and have been shown to be effective in man. Toxic effects such as agranulocytosis, aplastic anæmia and hepatic necrosis, of the occurrence of which animal tests gave no hint, have certainly been seen in man but these have been for the most part effects following repeated use. An anæsthetic is not administered repeatedly to the same person. It therefore seems to me that the initiation of clinical trials after the completion of a full investigation on animals offers no great problem of responsibility.

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Clinical Tests of New Drugs

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My approach to the testing of drugs is that of a clinical anæsthetist, which is bound to be a little different from that of the pharmacologist. Relationships with patients are concerned with considerations very different from those applying to animals; and the testing of new drugs may raise ethical problems of considerable difficulty.

The questions to be asked are these:

(1) What tests must I require to be made, on animals, before I try a new drug on humans?

(2) To what extent may species differences invalidate these tests?

(3) What risk is there that harm will befall the patient in spite of the best that I can do in screening?

In trying to define what is ethical, it is easy to draw up a code so strict that no experimentation at all would be permissible. That would reduce human pharmacology and therapeutics to a theoretical science. At the other extreme is the attitude which can be expressed like this: "in the anæsthetic room and the operating room we have unrivalled opportunities for the practice of applied pharmacology in the human. Let us exploit them to the full." Obviously, the correct attitude lies between these two extremes, and most anæsthetists would put it nearer to the first than to the second. Hence, before human experimentation is permissible with new compounds screening in animals must be as thorough as we can make it.

What is this screening expected to do? First, clearly, to enable us to reject compounds which are toxic to the animals used, and hence to *homo sapiens*. But of course all drugs that are active are "toxic" if we give enough. So we have to define more closely what we mean by toxic; and to do this we make use of the therapeutic ratio, the ratio of the effective dose to the lethal dose, to which Professor Burn has already

referred. We have to assume that the therapeutic ratio is about the same for man as it is for animals. If this assumption errs in one direction we may be led to reject a drug which could be useful: if it errs in the other we may endanger the lives of our patients. It is, therefore, pertinent to ask how valid is this assumption? For the general anæsthetics, as Professor Burn has said, there is a considerable body of evidence in favour of it; but anæsthetists are not concerned only with general anæsthetics. Indeed, with the obvious exception of halothane, the drugs added to the anæsthetist's repertoire during the last ten years have, in the main, not been general anæsthetics, but have belonged to pharmacological groups in which a species difference in therapeutic ratio may be expected. Careful comparisons have, therefore, to be made. If the comparison is between man and only one other species of animal, we should not put much faith in it. A lot depends, too, on *what* species of animal. The fact that a drug had a high therapeutic ratio in a frog would not embolden me to give it freely to a man. Should we, therefore, confine our screening to mammals and, pursuing the idea to its logical conclusion, even to primates? If we were to do this, experiment would be brought almost to a standstill; and the little that still went on would probably be no safer. For practical reasons, we have to accept the use of the laboratory animals: mice, rats, rabbits, guinea-pigs, cats and dogs: with more exotic creatures such as goats, monkeys, pigeons and goldfish forming a small minority. But we know that these species react differently to the relaxant drugs, for instance; and Professor Burn has reminded us that the cat's reaction to the opiates is very different from that of humans.

We know, too, that a twist of a molecule can profoundly alter its pharmacological effect, so that a narcotic, for instance, can be turned into a convulsant. It seems entirely possible, therefore, that subtle differences in enzyme chemistry existing between species might turn a harmless metabolite into a deadly one.

It seems to me that the answer to the second question is that the operation of species differences makes it impossible to be quite sure that a drug which has been shown to be safe for one—or even for several—species will be safe for man.

Safety, moreover, is not the only consideration when testing drugs for possible use in man. Side-effects must also be considered. It is usually possible to establish a technique for measuring the main effect of a drug: loss of reflexes, response to graded stimuli, fall of blood pressure, and so on; but side-effects are usually subjective and hence, in animals, immeasurable. By side-effects I mean, in this context, such things as nausea, faintness, disorientation, sleepiness, restlessness, euphoria, and liability to addiction. It is easy, in animal experiments, to draw up a series of dose-response curves and to put a number of analgesic drugs in order of potency; but even if this order should hold good for man, it could be that a drug with good analgesic powers exerted side-effects which rendered it useless as a therapeutic agent but of which the animal experimenter had perforce remained unaware.

We must realize, therefore, that animal screening—though it is unthinkable that it should not be conscientiously applied—has certain limitations. After the screening process has been completed there comes the next step of giving it to a human. This step must be taken by the clinician, and he has to bear the responsibility of it. Humans, in this context, may be of two kinds: healthy volunteers and hospital patients. In general, the former are not very much used, at any rate for active compounds. It is a nuisance to have one's laboratory boy out for the count; and medical students can put up with only so much. Moreover, for testing many remedies, it is essential to have a subject who is *not* healthy. It is obvious that some therapeutic agents can be tested only on patients suffering from reversible pathological conditions. But if we use patients, we are faced with the difficult problem of consent. Strict ethical considerations require that we should always obtain the consent of a patient before any experimental procedure and that for this the details and purpose of the procedure, and the risks it entails, should be fairly put to him. But things are often not so clear cut as this. If I decide to give a dose of a drug which is outside the recognized therapeutic range, or to use familiar drugs in an unfamiliar combination, or to test a new vaporizer or absorber, is that a matter for which consent should be obtained? And the patient is not the only person to be consulted. Anæsthetists seldom have charge of patients. Some other clinician, usually the surgeon, is involved as well. When we are cautiously trying a new relaxant, and the abdominal muscles grip the surgeon's hand so tightly that he can't move it, do we explain the position and ask him to bear with us, or do we say: "Don't worry. He'll be all right in a minute," and quickly slip in 50 mg. of suxamethonium? That depends on many factors; but obviously it is quite wrong to do anything which may endanger the patient, or in any way affect his welfare, without the consent of the surgeon who bears most of the responsibility for him. Most people would agree, too, that

one should not embark on human experiments unless the information which they will yield can be obtained in no other way; and unless they can be expected to yield a rich therapeutic reward. Mere scientific curiosity, laudable though that is, is not sufficient justification.

But given a case in which the goal is unassailable, and in which only human experimentation will suffice, one has to be mindful of the risks involved, and of the consequences of failure. In the history of therapeutics a number of instances may be found in which risks were run, with resultant benefit to mankind. The first vaccination might have been a failure and might have resulted in injury to the patient. In that event, immunology would have suffered a severe setback. For reasons which are obvious, it is difficult to find records of experimental work in which patients have been subjected to grave risks; but there are many examples of a research worker accepting grave risks when acting himself as the experimental subject.

The great John Hunter inoculated himself with gonorrhœal pus while investigating venereal disease. Carroll and Lazear allowed themselves to be bitten by mosquitoes carrying yellow fever, and Lazear died of the disease. Pettenkofer drank a culture of virulent cholera bacilli to show his contempt for Koch. August Bier, in 1898, had 2 ml. of 1% cocaine injected into his subarachnoid space, and got off with nothing worse than a headache. More recently, Pask submitted to considerable discomfort, and some risk, in investigating life jackets.

But of course work with the experimenter as the subject is governed by a different set of standards from those that can be applied to patients. Human experimentation, as distinct from work with animals, involves special hazards, and therefore requires special precautions and imposes special responsibilities.

However conscientious we are, it is difficult or impracticable to make our preliminary tests so thorough that we can rule out even the remotest complications. Nine or ten years ago Myanesin (mephenesin) was introduced as a muscle relaxant for intravenous use. Animal screening had been apparently adequate, and before the drug came into my hands it had been given to a number of patients with no untoward effects. The third patient to whom I gave it, for an interval appendicectomy, developed a lower nephron nephrosis, almost certainly as a result of intravascular hæmolysis, and died. Other cases of intravascular hæmolysis were later reported. It would, I suppose, have been possible to avoid this by animal tests for this specific purpose; but no one had entertained the possibility. A few years later, Efocaine was introduced as a long-lasting local analgesic and for a time it was much used, by perineural injection, to lessen post-operative wound pain. It was not until thousands of administrations without trouble had been reported that its propensity for destroying peripheral nerves, and for tracking back and damaging the spinal cord, was realized. Here again, animal work done *with this point in mind* would have prevented trouble, but it is easy to be wise after the event, and nobody thought of it at the time. It seems then that the answer to my third question: "What risk is there that harm will befall the patient in spite of the best that I can do in screening?" is that there is a small but definite risk.

The most difficult field of applied pharmacology which can concern anæsthetists is the evaluation of analgesic drugs; and there are several reasons why animal experimentation, in this field, is unsatisfactory. One reason is that it tells us nothing of side-effects as I have already mentioned. Another point, emphasized by Beecher, is that, in all experiments which can be devised, a reflex response is used as the criterion or end-point. But we have no means of knowing whether pain relief and depression of reflex activity in animals go hand in hand.

Hence for this work, though animal screening is an indispensable preliminary, the subject must be man. And this is where our difficulties start. There seems no doubt that pain produced in the laboratory is different from pain of pathological origin—from the pain of the hospital patient—and responds differently to drugs, so that hospital patients, *with pain*, constitute perhaps the only satisfactory material. In this field, more than in any other, we are perplexed by the placebo response; and if our evaluation is to be worth anything at all we have to arrange a double blind trial with three substances given in random order: the drug under test, an analgesic whose characteristics are known, and a placebo.

Even then we have to rely on subjective impressions, often relayed to us at second hand by people who may be biased or careless; and we have to find patients who really have pain. Then we find ourselves involved in the difficult ethical problem of palming off, on a patient we know to be in pain, a preparation we know to be devoid of pharmacological action. We can derive some comfort, in this dilemma, from the knowledge that in most series the placebo alone has conferred relief of pain in about one-third of the cases.

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*Frey, Kraut & Werle, 'Kallikrein,' Enke Verlag, Stuttgart, 1950.

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Proceedings of the Royal Society of Medicine Vol. 52 101

Section of Urology

President—ALEC W. BADENOCH, M.A., M.D., Ch.M., F.R.C.S.

Meeting
October 23, 1958

Injuries of the Ureter

PRESIDENT'S ADDRESS

By ALEC W. BADENOCH, M.A., M.D., Ch.M., F.R.C.S.
London

I HAVE chosen the subject of injuries to the ureter as I have been interested in it for many years and not very much time has been spent in discussing it in this Section: indeed, much less than it takes me to repair one injury. Terence Millin, in his Presidential Address in 1949, did of course digress on it when dealing more comprehensively with the ureter in gynæcology, but the only other occasion when the subject has been of surgical concern of recent years was at the meeting of the American College of Surgeons in London in 1954, at which I had the privilege of opening a discussion on these injuries.

Gunshot wounds.—Despite its rather delicate structure and tenuous length, the ureter is vulnerable in only very special circumstances. It is rarely injured by gunshot wound. Everidge and Barnes (1946) reported only 4 cases seen at a Base Hospital during the last war. In rather more than 10,000 casualties who were evacuated by air from Normandy and Belgium in 1944–45, and who passed through a Royal Air Force Hospital at which I was stationed, only one case of division of the ureter was observed.

A guardsman was first seen five days after being wounded. Through-and-through wounds of the stomach and small bowel had been treated by primary excision and suture at a forward hospital. On admission he was thought to have a residual abscess in the right iliac fossa. This was incised and drained and next day the diagnosis of a ureteric injury was obvious, as there was a profuse leak of urine from the wound. Intravenous and retrograde pyelograms confirmed this. Attempts at repair were unsuccessful and eventually a nephrectomy was performed.

I saw another intentional injury to the ureter last year.

A bank manager in Cape Town was shot in the abdomen whilst successfully intervening in an attempted robbery at his bank. The perforated bowel was repaired, extravasation from the injured ureter followed and this was drained locally and by nephrostomy. Despite this, the kidney had to be removed. I came into the case when, some months later, whilst convalescing in this country, the patient had an attack of right renal colic and was found to have two stones obstructing and causing dilatation of the remaining ureter. The calculi were removed, allowing the patient to continue his tour of Europe.

Closed injuries of the ureter are equally rare and I have encountered but two.

In 1933, a man of 36 was admitted to hospital following an attack of severe right-sided abdominal pain. A diagnosis of acute appendicitis was made, the abdomen was opened and the appendix was found to be a little swollen but not acutely inflamed. The peritoneum seemed a little œdematous, however, and after appendicectomy a drain was left down to the peritoneum. Next morning, there was an obvious discharge of urine from the wound. A plain X-ray showed a small opacity in the line of the ureter, and I was asked to do a retrograde pyelogram. I passed the catheter up to the opacity but no farther. Next day, he had another attack of colic and passed a small irregular calcium oxalate stone, and the fistula healed spontaneously.

Ten years ago, I was asked to see a case on behalf of an insurance company.

A young man had been involved in a road traffic accident, and the left side of his chest wall was stove in. Every rib on that side was fractured, he had a laceration of the left lung with a hæmothorax and very nearly died. By efficient resuscitation and aspiration of the hæmothorax he eventually made a very good recovery. Some three weeks later, there was brisk hæmaturia. An intravenous pyelogram showed no function on the left side and an attempt at a retrograde pyelogram failed, as the catheter was obstructed in its upper third. It was thought that the renal lesion was almost certainly associated with the injury but a neoplasm could not be excluded. His condition by now being reasonably satisfactory, a laparotomy was performed and the kidney was found to have been avulsed at the pedicle, the ureter being torn across just below the pelvi-ureteric junction. The atrophied remains of the kidney were removed without too much disturbance to the patient.

Scarring by fibrosis.—The ureter may be seriously obstructed as the result of fibrosis of the peri-ureteric tissue and pelvic fascia especially by irradiation, but a somewhat similar effect may occur after the extensive dissection necessitated by a radical hysterectomy.

A woman of 29 years, who had the uterus removed for a carcinoma of the body, was admitted to hospital some months later in a uræmic state with the blood urea raised to 250 mg. per 100 c.c. On retrograde pyelogram both ureters were seen to be dilated to the brim of the pelvis. The right ureter was transplanted into the sigmoid colon. The left kidney then completely suppressed but the transplanted right side, after several anxious days, took on the burden of renal excretion, sufficient for her needs until the carcinoma recurred.

I dealt with this case before ileal loop surgery became fashionable, but I am sure a conduit, perhaps with a later ileo-cystostomy, would be safer and more certainly effective than was the ureterocolic anastomosis. Occasionally, a ureter becomes partially obstructed by adhesions to an appendicectomy stump or to a calcified gland and may give rise to sufficient symptoms to require adhesiolysis, or some other form of intervention.

These injuries are all comparatively rare and whilst of interest do not constitute the main premises of my Address. This is concerned with injuries to the ureter which occur accidentally in the course of a surgical operation. I have excluded those divisions which we make deliberately in the operation of partial and total cystectomy, and also those which we may make intentionally or occasionally accidentally as when a ureter is intimately adherent to a diverticulum.

Surgical injuries.—The large majority of unintentional injuries to the ureter with which I have been concerned have followed operations in the pelvis.

On the other hand, I have seen one case (*see* p. 103) where a piece of ureter 4 cm. in length was removed in mistake for the lumbar sympathetic chain.

A woman suffered from stress incontinence for five years and the late Wilfrid Shaw performed his rather intricate hammock operation with complete success for the stress incontinence. However, she now began to have intermittent attacks of pain followed by discharge of pus from the vagina and sometimes incontinence. After repeated investigations over many weeks she was found to have the upper ureter of a right double kidney opening into the vagina. She had not had any similar trouble or true incontinence prior to the sling operation and we decided this ureter had in some way been divided. A heminephrectomy was followed by relief of symptoms.

A patient had worn a vaginal ring pessary continuously for a number of years. With some difficulty it was removed and this procedure was followed by incontinence which was at first thought to be due to a vesico-vaginal fistula but the latter communicated with the left ureter. This was mobilized, divided at the site of the fistula, and re-implanted in the bladder with a satisfactory result.

Including the cases I have already mentioned, I have had dealings with 48 cases of injured ureter (Table I). 4 cases followed abdomino-perineal excision of the rectum. Injury occurs only rarely in this operation. Cooling (1958) in analysing a series of 369 cases of excision of the rectum found only 4 cases of injury. In 2 the ureter had been ligated accidentally, and in 2 deliberately. 39 injuries occurred during gynæcological operations and I may say that these operations were performed at sixteen different hospitals. In the large majority of cases hysterectomy, either total or radical, was the operative procedure (Table II). The incidence of these injuries has been worked out at a number of centres. Ureteric fistula is of comparatively common occurrence in the radical operation. Liu and Meigs (1955), in analysing a series of 473 radical operations from a group of Boston hospitals, found 45 fistulæ, i.e. 9%. On the other hand, Newell (1939) found the incidence to be only 0·4% in 3,144 cases of hysterectomy of various types. In the years 1952–1954 inclusive, in a careful analysis by Ostry (1955) of 857 hysterectomies performed at the Samaritan Hospital, six ureters were injured, giving an incidence of 0·7%. At the same hospital, during a consecutive period of six years, 3,172 operations were performed in which the ureter was liable to injury. In only 11 cases (0·34%) was an injury known to occur. In fairness to my colleagues, I should mention that in some of those cases the operation was performed by a surgeon under training. Nevertheless, the complication does occur even when the operator is a highly skilled and experienced surgeon. As John Howkins (1954) has said: "the gynæcologist who boasts that he has never damaged the ureter is either guilty of under-statement or has a small and timid practice." It is incumbent on all of us, therefore, who work in the pelvis to take every possible care to avoid such an injury. It has been suggested that a patient should have each ureter catheterized before undergoing hysterectomy. I cannot feel that this is necessary. Indeed, the procedure may give rise to a false sense of security as the ureter has been divided, and also

TABLE I.—INJURIES TO THE URETER

Gynæcological operations	39
Abdomino-perineal excisions	4
Gunshot wounds	2
Lumbar sympathectomy	1
Avulsion	1
Rupture from stone colic	1
Total	48

TABLE II.—OPERATIVE PROCEDURES CAUSING FISTULA

Total hysterectomy	22
Wertheim radical hysterectomy	10
Pelvic floor repair	3
Rupture of full-term uterus	1
Amputation of cervix	1
Sling for stress incontinence	1
Removal of vaginal pessary	1
Total	39

ligatured, with a catheter *in situ*. A preliminary excretion urography will help in ascertaining the anatomy in the particular patient, but meticulous attention to the steps of the operation is the most important preventive factor. The ureter can be nicked with a needle, clamped, or divided and, apart from these hazards of direct assault, the blood supply can be interfered with and ischæmia produced in the lower end. This is especially so in the extensive dissection required in the radical operation. Howkins (1954) emphasizes the danger points in the course of the ureter, the most important of which are:

(1) When it enters the pelvis and is crossed by the ovario-pelvic fold of peritoneum.

(2) When it passes downwards, forwards and medially in the base of the broad ligament and passes beneath the uterine vessels.

At any part of its course, however, it may be injured by tearing the peritoneum to which it is closely attached and more especially it can be occluded, in part or in whole, by over-enthusiastic clamping or suturing in an attempt to stop troublesome bleeding. In the large majority of my cases the injury has been at the lower end. In more than half I have removed catgut or silk from the region of the injury, therefore ligature or suture is the commonest cause in this series. Ischæmia may occur when there has been extensive dissection of the ureters, and division of the many blood vessels which supply it, as in the radical operation.

Hanafee *et al.* (1958) have recently done an excellent radiological survey after the radical operation. In the immediate post-operative period X-rays may not be of much value because there is always some degree of ileus leading to an accumulation of gas and, furthermore, the kidneys do not seem to be able to concentrate the dye very well. Bilateral hydronephrosis and atonic bladder are commonly found in the early stage. Cystograms show what they call the "Christmas tree" or pyramidal shaped bladder, and there is a large amount of residual urine. The distal 4–5 cm. of ureter may be of normal calibre or even narrowed but the upper part is usually dilated. These changes can be caused by interference with the blood supply. In the radical operation, the internal iliac arteries are often ligatured as are the superior vesical, uterine, inferior vesical and middle hæmorrhoidal arteries. It is indeed fortunate, as Daniel and Shackman (1952) have demonstrated, that the ureteric blood supply is so generous. All these vessels supply branches to the distal end of the ureter and to the posterior, inferior and lateral portions of the bladder. It is an axiom that the more extensive the removal of potential cancer-bearing tissue, the greater is the likelihood of injury to a normal organ. Hanafee *et al.* (1958) have found that many of these injuries recover after a period of weeks, but in some, necrosis occurs with resultant fistula formation. In my own series, 4 fistulæ were almost certainly ischæmic in origin.

Clinical Course

(*a*) *Observed at operation.*—The clinical course of a ureteric injury depends on whether or not it is seen at operation. Cases are on record of a clamped ureter having been observed at operation. I have not had such a case but it is then advised that the clamp should be released and a ureteric catheter passed up to the kidney and left in for some days. I think the observation of this injury must be extremely rare. If the ureter is seen to be divided near the bladder, it should then and there be re-implanted in that organ. I have been told of several successful cases of this manœuvre but have not included any in my series. Two unsuccessful immediate implants are, however, included. If the ureter is seen to be divided near the brim of the pelvis, unless the patient is in desperate straits, an attempt should always be made to restore its continuity by suture over a catheter. I have not performed this personally, but 4 such cases are included in this series: 3 were successful, 1 subsequently required nephrectomy.

Many methods of anastomosis have been employed—end-to-end, side-to-side, and end-to-side, and Charles Higgins (1935) has reported success after the cut end has been joined to the side of the normal ureter. Experimentally, however, Hamm and Weinberg (1957) found that the most satisfactory method was by directly joining the ends after they had been cut obliquely in a somewhat spatulate fashion. The consensus of opinion is in favour of leaving a catheter or polythene tube in the ureter, drawing this out through the bladder and attaching it to a Foley catheter, which is then left to drain the bladder. Ligation of the observed divided ureter is rarely indicated but may be the most reasonable solution if a large segment of the tube has been removed. I know of some cases when this has happened in association with carcinoma of the sigmoid colon. One unusual case I have already referred to.

A lumbar sympathectomy was being attempted in a fat young woman, and some 4 cm. of ureter was removed from the upper segment. The surgeon in this case, although quite senior, was still in training. His chief, in the adjoining theatre, was informed and attempted to restore the continuity but owing to insufficient length was unable to do so and ligatured the upper end. I saw the patient next morning, her general condition was satisfactory, she had passed 15 oz. of urine and an intravenous pyelogram which had been suggested, showed that the remaining kidney was quite normal. It was decided to do no more.

(*b*) *Not observed at operation.*—If the ureter has been injured and this is not observed, the post-operative course will be variable and will depend on several factors. If both ureters are occluded, there will be anuria, no urine will be passed and the bladder will remain empty, certainly after the first post-operative catheterization. One or both ureters may form a fistula. There are three bilateral injuries in my series. One had both ureters obstructed following a pelvic floor repair. One had anuria following bilateral ligature at the brim and the third had the left ureter occluded by ligature and the right one divided. I will refer to these again later.

Unilateral injuries vary tremendously in their manifestations. If the ureter is tied off, the kidney may remain completely obstructed. In some cases, especially if infection is present, there is pain in the loin and raised temperature, but in some, symptoms are minimal and patient and surgeon remain ignorant of any injury, maybe for a long time.

A woman who had had a hysterectomy nine years previously returned to her surgeon's out-patients, complaining of a swelling in the right side of the abdomen. He found the right kidney easily palpable and enlarged. An intravenous pyelogram showed a normal left side, but no function on the right. She was referred to me and I confirmed the clinical findings. An attempt at retrograde catheterization failed as the catheter was obstructed 4 cm. from the ureteric orifice. I explored the right kidney and ureter and finding the kidney but a shell and the ureter dilated the whole way down to the obstruction, I did a nephro-ureterectomy. Everything went well until she became mobile and walking about in the ward. She then said "you may have removed my kidney but the swelling is still there". My chief assistant found that what she had really complained of was a small intramuscular lipoma and when this was excised she was quite happy.

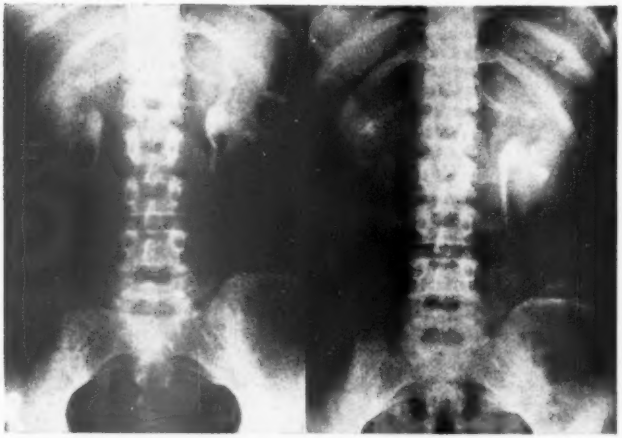
In one of this series there was extravasation into the left iliac fossa following a left salpingo-oophorectomy.

The patient had previously had a hysterectomy and other pelvic operations. She had had some loin pain and pyrexia and on the seventeenth post-operative day a swelling was found in the left iliac fossa which proved at operation to be a collection of urine. After a very lengthy exploration the proximal end of the ureter was found just below the bifurcation of the iliac artery and was tied off as the lower end was never identified. I saw her the following day and we decided to leave it. She made an uninterrupted recovery.

Another patient had aching pain in the loin following total hysterectomy which continued for three months. An intravenous pyelogram showed no function on that side. The ureter was blocked 3 cm. from the orifice. The kidney was explored and a nephrectomy performed. There was no evidence of hydronephrosis, the pelvic capacity being only some 10 ml., but the capsule was very adherent to the perinephric fat and there were widespread pyelonephritic changes throughout the kidney.

Fistula formation.—In my series 32 of the 39 gynæcological injuries formed a fistula. In many the immediate post-operative period was rather stormy, some degree of ileus was common, pyrexia was usually present as also was lower abdominal pain. Loin pain was not a marked feature but when it did occur it was often intense and indeed resembled ureteric colic. In each of the cases which experienced severe pain, the injury was incomplete and the pain may well have been caused by the ureter being caught by a suture, part of which was in the lumen, and spasm occurring in an attempt to extrude the foreign body. The pain cleared up dramatically when the fistula developed. As one resident put it to me "she is very much better to-day, but can't hold her water". In this series 20% of the fistulæ appeared in the first week, 60% in the second and 20% in the third week or later. The longest interval from the time of operation until establishment of a fistula was twenty-four days. The early fistula is from division or partial inclusion in a suture, the in-between fistula, from ligation, with actual division or subsequent sloughing, and the late one is from ischæmia.

Determination of cause and side of fistula.—The diagnosis of fistula is of course easy but it may be extremely difficult to decide whether the leak is from the bladder or from a ureter, and if from a ureter, from which side. An intravenous pyelogram should always be done and very often gives an important pointer. One side will be normal, and the other may show a little dilatation of the renal pelvis and upper ureter (Fig. 1 A, B). There may be obvious extravasation at the lower end of the ureter in the perivesical space (Fig. 2). Cystoscopy can be very helpful and should always be carried out; an irrigating cystoscope is essential. In the immediate post-operative phase, in both intraperitoneal and vaginal operations, there is much œdema at the base of the bladder. The heaped-up, reddened mucous membrane makes the identification of the ureteric orifice difficult and sometimes impossible, and in at least one case led to the diagnosis of papillomatosis of the bladder. If at all possible, an attempt should be made to catheterize each ureter. If vesico-vaginal fistula is suspected, the vagina should be lightly packed with gauze and 1 ml. of 0·4% indigo carmine in 200 ml. of water should be injected into the bladder. If the bladder and vagina communicate, the gauze will show a blue stain. If it becomes damp without staining, the fistula is undoubtedly ureteric.



A B

FIG. 1.—A, Normal pyelogram before operation. B, Hydronephrosis on right side indicative of injury to this side with post-operative fistula.

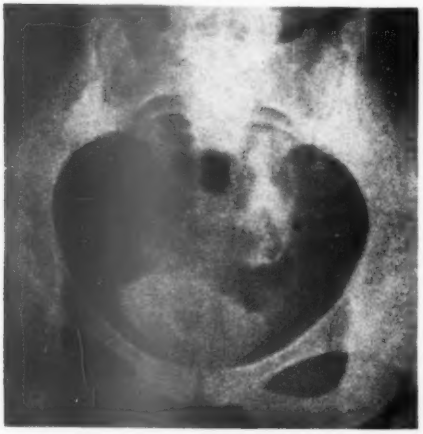


FIG. 2.—Dilated left ureter connecting with extravasation.

TREATMENT

In bilateral injuries this may be imperative as it was in 2 of my cases.

The first followed a pelvic floor repair. I saw her forty-eight hours after operation when there was complete anuria. Cystoscopy showed an œdematous bladder base, and neither orifice could be seen. All the sutures in the vagina were removed, and she made an uninterrupted recovery. Happily, despite the removal of all the sutures, I believe the operation proved effective and she no longer had a prolapse. It must be emphasized that all the sutures have to be removed.

The second case had anuria following a total hysterectomy and bilateral nephrostomy was performed. As a rule unless the patient is in dire straits I would rather remove the ligatures and would expose first one ureter extraperitoneally at the bifurcation of the vessels, work down to the obstruction and release and repeat the procedure on the other side. In this case, however, the nephrostomy turned out to be the better approach, since it was found that both ureters had been ligatured at the brim of the pelvis. A repair was effected on each side and the left became almost normal. A uretero-vaginal fistula developed on the right side. A catheter could be passed easily up this side without obstruction at the site of repair. This fistula leaked for weeks at a time, although it also sometimes remained closed for weeks. I saw her some eighteen months after the original operation and advised exploration of the lower ureter. At operation, a partial injury of the ureter was found and the ureter was divided and re-implanted. She became dry and two months later had a good functioning kidney still with some hydronephrosis. Subsequently, an intravenous pyelogram showed both kidneys had almost returned to normal. This patient must, therefore, have had two injuries to the right ureter as well as one to the left.

My third case of bilateral injury followed a Wertheim for carcinoma in a woman of 33 years. She passed no urine from the bladder but leaked from the vagina from the third day. I first saw her fourteen days after the injury and an intravenous pyelogram then showed function with hydronephrosis on the right side, but no evidence of function on the left. The bladder contained pus but no urine. A catheter was obstructed low down in each ureter. The patient was ill, cachectic with an infected, discharging wound. It was decided to wait until the sepsis had abated before attempting restorative surgery. It was eleven weeks and four days before this took place. At operation, I found the right ureter had formed a uretero-vaginal fistula and the left was completely occluded by a ligature. I re-implanted both ureters into the bladder. The convalescence was stormy, but she was a good patient and the nursing staff were determined that she should live and that she should be dry. They succeeded. A pyelogram taken eight weeks later showed both kidneys were functioning and one taken three years later showed two normal kidneys. She was free from symptoms and, as far as one could tell, free from carcinoma.

How long can a kidney survive after the ureter has been completely occluded? We really do

not know a great deal more about it since Hinman's masterful study of 1934. He then found experimentally that a rabbit's kidney did not atrophy if the ureter was tied off, unless infection was present. It developed a hydronephrosis which gradually increased in size until the kidney tissue became thinned out like a shell. This may well have been what happened in the kidney of the woman whose symptoms were due to a lipoma but I agree with O'Connor (1956) who says that complete sudden ligation is usually followed by symptomless atrophy. I feel that the result in the patient whose kidney became normal after eighty-one days' occlusion of the ureter, rather refutes Hinman's postulation. In the pyelogram taken eight weeks after the double implant the kidney showed no evidence of hydronephrosis and the calyces, indeed, were quite normal. Furthermore, the kidney function was excellent and eventually completely recovered. I have felt for a long time that the view that twenty-one days' occlusion will lead to permanent suppression is not correct, and certainly in this case it was not so, although perhaps this result was influenced by the fact that the other kidney was not functioning normally. I can find very little reference to clinical cases but Reisman *et al.* (1957) reported one case of unilateral injury which recovered normal function when the ureter had been ligatured for thirty-three days.

In my series there were 30 cases of unilateral injury producing fistula; 2 of these had in addition a vesico-vaginal fistula, and 1 a fistula of the sigmoid colon. In 6 cases, a ureteric catheter could be passed up to the kidney. In 2, the catheter was left in for twenty-four hours, in the other 4 it was removed. All these cases healed spontaneously within a fortnight. One case healed spontaneously without catheterization. I had always felt that if I failed to get a catheter up the ureter, operation was necessary and in such cases of fistula it has been my practice to explore the ureter. My colleague, Mr. J. Burke of St. James' Hospital, however, has had 2 cases with good, though not perfect, results, which he has treated conservatively after having failed to get the catheter up the ureter.

The first case had had a synchronous combined abdomino-perineal excision of the rectum. She had a stormy convalescence and twenty-three days after operation developed a fistula. An intravenous pyelogram taken before the operation was normal. One taken five weeks after operation, after the development of the fistula, showed no function on the right side. A catheter passed easily up the left side, but on the right it was obstructed at 10 cm. A picture taken after injection of dye showed extravasation, displacement of the ureter but also filling of the proximal ureter. In view of this, it was decided to wait. The fistula closed, leaving some dilatation of the renal pelvis on the right side, but nine months later she was free from symptoms and there was no increase in the dilatation.

The second patient had a fistula following a pelvic floor repair. There was a bilateral hydronephrosis, and neither side could be catheterized, thirty-three days after operation. Following the attempt at catheterization, she remained dry; nine months later she was free from symptoms and both kidneys functioned well although there was some dilatation at the lower end of the left ureter.

When a fistula which has healed spontaneously has taken many weeks to do so, and especially if associated with bouts of pyrexia and loin pain on the affected side, the kidney is usually infected and may indeed have ceased to function as in one of the Boari repairs in this series. Usually little is gained by waiting if the ureter is occluded and it is thought that operation will eventually be necessary.

In one unilateral case, interference became imperative. On the fifth day after a total hysterectomy, the patient leaked urine *per vaginam* and continued to do so for some thirty-six hours. She then became dry but began to complain of abdominal pain. When I saw her a few hours later, she was tender in the left iliac fossa. There was much guarding and some rigidity on the left side and at operation it was found that a divided ureter was leaking into the peritoneal cavity. The result in her case was very good. After three months the kidney on the injured side was quite normal whilst the other side showed some hydronephrosis. A picture taken nine years later showed that the injured side had remained satisfactory but on the other side the hydronephrosis had progressed.

The approach I most often employ is through an Abernethy extraperitoneal exposure, although not infrequently I inadvertently open into the peritoneal cavity. Dissection is always difficult and a plane of cleavage almost impossible to find. A hæmatoma is not uncommonly encountered. The operation is long and tedious and the ureter can be extremely difficult to find. It is wise to identify the bifurcation of the iliac artery as soon as possible; the ureter can then be identified and followed downwards. It is usually dilated. In the early days, after division or ligature, there is marked œdema of the peri-ureteric tissues and a swelling as thick as a little finger may be found with a ureter of normal calibre forming its core. Sometimes, and especially in the later stage, the ureter is dilated and it has then a rather bluish appearance and may be mistaken for a vein. An ischæmic ureter is usually dilated, flabby-looking and grey, and vermiculation is absent. A tied-off ovarian vein may bear some resemblance to an ischæmic ureter. There is certainty of the identity of the structure when urine is seen to spurt out of the tube. It should be followed as far down to the vagina as possible, in order to

conserve length and if this is done, in the large majority of cases, it can be re-implanted in the bladder. I have no doubt that it is the safest and surest procedure to conserve the kidney, if this can be effected. In this series of 23 fistulæ treated by operation, 19 were re-implanted directly into the bladder wall, with 17 permanently successful results (Figs. 3 and 4). In 2, the fistula persisted or remained; a second nephrectomy was performed in one, and in the other a uretero-ileal cystostomy was made. The cut end of the ureter should be implanted into the nearest part of the bladder wall. I used to split the lower end, forming two flaps which were sutured back into the bladder mucosa, and this can give very good results as in a case treated by my colleague Mr. H. K. Vernon.

A woman of 45 had a total hysterectomy and bilateral salpingo-oophorectomy. After the operation, she passed no water from the bladder but leaked from the vagina. At cystoscopy, the ureteric orifices could not be identified on account of œdema. An intravenous pyelogram showed considerable hydronephrosis on each side. Twelve weeks later Mr. Vernon re-implanted both ureters by the flap technique with a perfect result.

For some years, when the calibre of the ureter is normal, I have used a direct implant and when the ureter is dilated, a mucous membrane to mucous membrane anastomosis. I stitch the bladder muscle to the peri-ureteric tissue with several interrupted sutures, rather like a Witzel gastrostomy. This is usually easily done because of the thickness of the tissues surrounding the ureter. As in all plastic procedures, tension and constriction must be avoided. I do not use a catheter in the ureter implanted in the bladder. I have not used the method described by Patton (1952) of St. Louis, when the cut upper end is brought through the lower end to present at the ureteric orifice. It must be very uncommon for sufficient length of ureter to remain for this to be done without tension.

When I have found it impossible to approximate the ureter and bladder, I have raised a flap after the manner described by Casati and Boari (1894). This method has been employed three times in this series; only one case was satisfactory. The second case required a secondary nephrectomy twelve months later for chronic pyelonephritis producing persistent pain and infection. In the third case the fistula recurred twice and closed

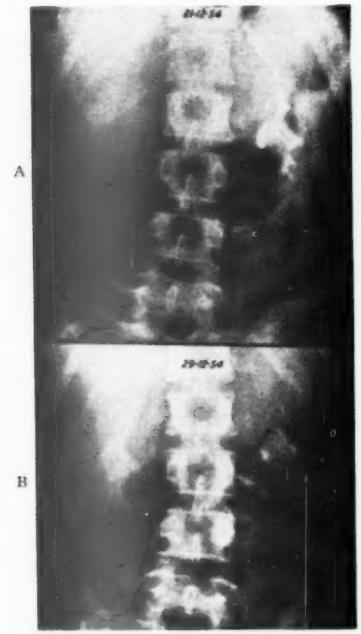


FIG. 3.—A, Intravenous pyelogram five days after hysterectomy with no excretion on right side. B, Intravenous pyelogram eight days after development of fistula, showing hydronephrosis.

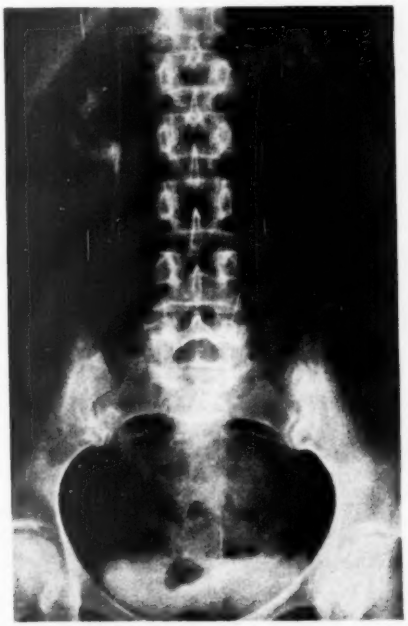


FIG. 4.—Two months after implant of right ureter.

gradually over a period of three months. Now, twelve months after the Boari operation, she is free from symptoms but there is no evidence of function on this side. I therefore cannot say I am enamoured of this operation. I have employed an ileal loop in one failed anastomosis, with an ischæmic ureter. Convalescence was most satisfactory and three months after, she was well and free from symptoms. However, an intravenous pyelogram showed very poor function on this side.

Results.—The results of treatment of this serious injury are not nearly as pessimistic as some published reports would indicate. In this series of 48 cases of injury to the ureter, there have been no deaths. Over 80% of the cases of fistula have healed with good renal function (Table III).

TABLE III

Healed spontaneously ..	7	22%
Healed after operation ..	19	59·25%
Primary nephrectomy ..	2	6·25%
Secondary nephrectomy ..	4	12·5%

Nevertheless about a fifth of these cases have lost a kidney either by nephrectomy or by suppression of function. In one of these at least, it was the combination of an impatient patient and an impetuous surgeon and I have no doubt that when a ureteric injury does not early show signs of spontaneous closure, there is more chance of the kidney being conserved if the surgeon who did the original operation passes the patient to a urological colleague.

We all realize that even when the most careful technique is employed by a skilled surgeon, injury to the ureter can occur. Especially is this so in the extensive and formidable operations performed to extirpate cancer, from what Sir Gordon Gordon-Taylor has called the Fairyland of Surgery. The injury usually becomes obvious and the persistent fistula remains distressing to the patient and to her attendants until it has closed. With careful investigation and cautious treatment, in most cases it should and can be closed and the patient left with a normal upper and lower urinary tract.

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Meeting
November 27, 1958

THE following specimens were shown:

Twin Diverticula of the Female Urethra.—Mr. J. C. ANDERSON.

Renal Adenoma.—Dr. J. H. EARLE.

(1) Tuberous Sclerosis with Bilateral Renal Tumour. (2) An Unusual Large Hernia of the Bladder (a Scrotal Cystocele).—Mr. R. A. MOGG.

Intravesical Foreign Body (Gordian Knot in Plastic Tube).—Mr. C. I. MURPHIE (for Mr. J. E. SEMPLE).

Scrotal Emphysema.—Mr. C. I. MURPHIE.

Transient Ring-constriction of the Bladder.—Mr. JOHN HOPEWELL.

Malakoplakia of the Bladder.—Mr. KENNETH OWEN.

Partial Cystectomy for Localized Leukoplakia of Bladder.—Mr. F. P. RAPER.

Carcinosarcoma of the Bladder.—Mr. D. INNES WILLIAMS and Dr. R. C. B. PUGH.

Radium Necrosis of Bladder Following Radium for Artificial Menopause.—Mr. D. M. WALLACE.

Ureteric Ectopia.—Mr. J. C. ANGELL.

Bilateral Mega-ureter in a Child of 4.—Mr. R. O. LEE.

Calculi in the Seminal Vesicle, Associated with a Hypoplastic Kidney.—Mr. W. G. Q. MILLS.

Sarcoidosis of Epididymis.—Mr. B. H. PAGE.

Rhabdomyosarcoma of the Bladder in a Boy of 4 Years.—Mr. R. F. POWER (for Mr. F. R. KILPATRICK).

Rhabdomyosarcoma of the Epididymis.—Mr. R. F. POWER (for Mr. HARLAND REES).

Lipoma of the Spermatic Cord.—Mr. ALEX E. ROCHE.

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Antacids in Peptic Ulcer. *The Practitioner*, January 1956, **176:** 103

Recent Advances in the Ulcerative Diseases of the Gastrointestinal Tract. *Amer. J. Gastro.*, December 1956, **26:** 665

Ambulatory Continuous Drip Method in the Treatment of Peptic Ulcer. *Amer. J. Dig. Dis.*, March 1955, **22:** 67-71

Management of Peptic Ulceration in General Practice. *Med. World*, December 1954, **81:** 591-601

Clinical Investigation into the Action of Antacids. *The Practitioner*, July 1954, **173:** 46

Further Studies on the Reduction of Gastric Acidity. *Brit. Med. J.*, 23rd January 1954, **1:** 183-184

Control of Gastric Acidity by a New Way of Antacid Administration. *J. Lab. & Clin. Med.*, 1953, **42:** 955

The Effect on Gastric Acidity of "Nulacin" Tablets. *Med. J. Aust.*, 28th November 1953, **2:** 823-824

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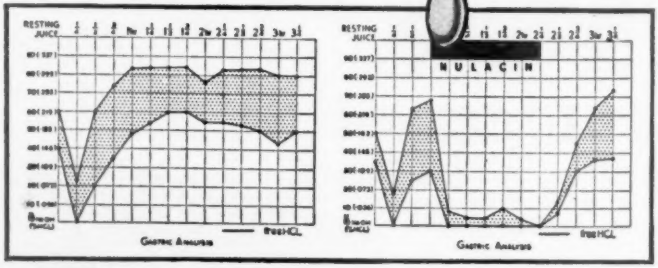
(Medical Times 1958, **1**, 74)



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Section of Epidemiology and Preventive Medicine

President—Sir JAMES KILPATRICK, K.B.E., C.B.

Meeting
October 17, 1958

SYMPOSIUM ON TETANUS

Sir John Boyd (London):

Tetanus in Two World Wars

Tetanus, resulting from the contamination of a wound with soil or other material bearing the spores of *Clostridium tetani*, is one of the grave hazards with which the battle casualty is faced. The risk varies with the nature of the soil over which the battle is fought, being greater in agricultural countries such as Flanders, and less in sandy localities such as the Western Desert. Table I gives the incidence in different campaigns; the figures up to and including 1914–1918 are taken from the official history of the First World War, while the remainder were compiled by the author from official documents.

TABLE I

	Per thousand
British Legion in Spain (Peninsular War)	12·5
Crimean War	2·0
American Civil War	2·0
Franco-Prussian War	3·5
Western Front, 1914–1918	1·47
B.E.F., 1939–1940	0·43
Middle East Force, including Malta ..	0·22
British North African Force	0·04
Central Mediterranean Force	0·09
N.W. Europe, 1944–1945	0·06

These figures can be placed in three categories.

(1) Up to the end of the Franco-Prussian War, before specific prophylaxis of any kind was available. The varying incidence rates during this period can be attributed to the terrain.

(2) The First World War, when passive immunization with tetanus antitoxin was used.

The overall figure of 1·47 per thousand does not give the full picture.

From August to October 1914 there were no definite regulations about the administration of antitoxin, and many wounded men were not given it. The incidence during this period was around 8 per thousand.

From mid-October onwards, every wounded man was given 1 dose of 500 units of antitoxin. This produced an immediate reduction in the incidence to 1 per thousand, but subsequently there were fluctuations, the figure in some months reaching 3 per thousand. In June 1917 an increase in dosage was ordered, each man being given 4 injections of 500 units at weekly intervals. This brought the incidence down to 1 per thousand, at which level it remained until the end of hostilities.

These results were encouraging, but serum prophylaxis had obvious shortcomings. There was frequently unavoidable delay in administering the antitoxin; it failed to prevent "delayed" tetanus, and in many cases it produced serum sickness, sometimes quite severe.

Ramon and Zoeller (1927, *Ann. Inst. Pasteur*, **41**, 803) discovered that active immunization could easily be achieved by administering tetanus toxoid, i.e. toxin treated with formalin, which as a result has lost its toxic but not its antigenic properties. Experiments at the Royal Army Medical College confirmed this observation, and demonstrated the advantage of leaving an interval of at least six weeks between the first and second doses, and a further interval of three to six months until the third or "booster" dose was given.

(3) In the Second World War, both active and passive immunization was used. At first, only 2 doses of toxoid were given; later, it became possible to give a third dose, and ultimately, everyone was given a booster dose once a year. In addition, every wounded man was supposed to be given 1,500 units of antitoxin, but it seems probable that this instruction was not always carried out.

The figures in Table I testify to the success of these measures, and indeed understate it, as many of the cases which make up these percentages were in the small minority who succeeded in "dodging" inoculation. Thus, all the cases in B.E.F., 1939–1940, fall into this category, as do 3 of the 6 cases which occurred in 1944–1945.

While other causes such as the use of sulphonamides and penicillin may have played a minor role in preventing tetanus, there can be no reasonable doubt that active immunization was mainly responsible.

Two points are worthy of note. The mortality rate in immunized men was not significantly lower than it was in unimmunized men. Secondly, the incubation period in immunized

men who developed tetanus was, in practically all cases, less than ten days, suggesting that this is the danger period, and that antitoxin given immediately after the wound is inflicted may therefore be of advantage. However, in the U.S. Army, where everyone was actively immunized, and each wounded man was given a further dose of toxoid, and no antitoxin, the results were similar. There is little doubt that the important thing is to ensure that everyone is fully immunized before he is wounded. Subsequent immunization is then probably of secondary importance.

Dr. E. M. Mackay-Scollay (Stafford):

An Outbreak of Post-operative Tetanus

Outbreaks of post-operative tetanus in Great Britain are fortunately rare. Most of the reported episodes have concerned one or two cases, but exceptions to this generalization were the Edinburgh outbreak (Mackie, 1928) and the events at the Royal Infirmary, Stoke-on-Trent, early last year. At Stoke, 5 cases occurred over an operation period of five days; 2 proved fatal.

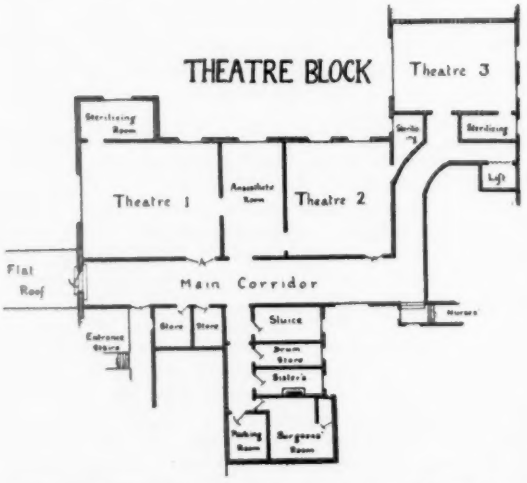
I was asked to join Dr. C. R. Knappett in an investigation into the causes of the tragedy. I propose recounting our joint findings, together with the results of some interesting serendipity. Although we carried out our work independently in our respective laboratories, many of our results were in confirmation or in extension of each other's work.

The Royal Infirmary is one of two general hospitals in Stoke-on-Trent. It has 455 beds. The operation lists are heavy and the bulk of the surgery is performed in the main theatre block, which comprises three theatres and ancillaries, and it was in this block that all the operations complicated by tetanus were performed. The block was confined to the first floor and from the plan of the site (Fig. 1) it is seen that there were three modes of access: by lift at one extreme of the main corridor, and by two adjacent doors at the other. One of these served a staircase; the other gave on to a flat roof which in turn led to the grounds of the hospital. The nurses' and surgeons' changing room annexes had no independent exits.

Theatres 1 and 2 shared a common anæsthetic room and a common ventilation system of the extraction type. All three theatres had separate instrument sterilizing rooms, but all three shared the same system and practice of gown and glove sterilization. The walls of the theatres and attached rooms were tiled and the floors terrazzo. The ceilings were paint on plaster. The nurses' changing rooms were in sound condition but the surgeons' annexe was in poor repair with rents in wall plasters and defections in the ceilings.

TABLE I.—CASES OF TETANUS IN ROYAL INFIRMARY, STOKE-ON-TRENT, RELATED TO THE NUMBER OF OPERATIONS PERFORMED, FEBRUARY 21–26, 1957

	Theatre						Tetanus cases	Total operations
	1		2		3			
Thursday Feb. 21	1st	7	2nd	7	—		2	14
Friday Feb. 22 . .					3rd	3	1	22
Saturday Feb. 23			4th	10			1	16
Sunday Feb. 24. .							—	1
Monday Feb. 25	5th	9					1	22
Tuesday Feb. 26	Onset of tetanus in 2nd case				Totals		5	75



[FIG. 1.—Diagrammatic plan of the main theatre block of the Royal Infirmary, Stoke-on-Trent.

The first patient (Case II) to develop symptoms of tetanus did so on February 26 following an operation for perforated appendix on February 21. Initially, he was regarded as a case of endogenous infection, but, two days later, a second and a third patient developed tetanus and it was evident that a disaster had occurred. The theatres were closed, furniture was concentrated in Theatre I, and the whole block was subjected to a full-scale regime of scrubbing and cleaning. A scheme of mass prophylaxis with 50,000 units ATS was begun on all patients who had been operated upon

in the block during that and the previous week. The full extent of the outbreak is apparent in Table I.

Two facts immediately present. Firstly, that the outbreak involved patients who had been operated upon in all three theatres; and secondly, that the unit was an extremely busy one. In fact, with the staff available, the block was working to capacity.

A further 56 operations were performed between February 25 and February 28, when the theatres were closed. A total of 131 operations were performed between February 21 and the closure of the unit.

Reference to the data concerning the individual cases (Table II) yielded no information which might be considered epidemiologically significant.

TABLE II.—POST-OPERATIVE CASES OF TETANUS IN THE ROYAL INFIRMARY, STOKE-ON-TRENT, 1957

Case	1	2	3	4	5
Age	50	57	43	52	41
Sex	F	M	M	M	F
Operation ..	Colpo-perineo-rrhaphy	Appendi-cectomy (perfor-ated ap-pendix)	Appendi-cectomy (chronic appen-dix)	Hæmo-rrhoid-ectomy	Ventro-suspen-sion
Date of oper-ation	Feb. 21	Feb. 21	Feb. 22	Feb. 23	Feb. 25
Onset of tet-anus	Mar. 1	Feb. 26	Feb. 28	Feb. 28	Mar. 3
Incubation (days)	8	5	6	5	6
Outcome ..	Recovery	Recovery	Death	Death	Recovery

When I joined the investigation on March 8, the problem presenting was twofold, firstly, to discover the source of tetanus spores, and secondly, to determine the vehicle of infection.

To achieve the first, a survey was made of the theatre block, its ancillaries, the location of the plant and the method of sterilization of the dressings, gowns and gloves, and the mode of transport of drums to and from the theatres.

Samples of dust and debris were taken from theatre furniture, floors, walls and shelves throughout the block and from points in the ventilation system. All types of catgut in use, all dusting and therapeutic powders, whether sterilized or not, instruments, and all packed drums as found on the morning of March 1 were examined. Unfortunately, both sterilized and unsterilized glove drums were impounded together.

During sampling in the theatre block, particular attention had been paid to damaged plaster in the surgeons' annexe where actual tufts of animal hair used in the plaster preparation were sticking out (Sevitt, 1949). Dr. Knappett carried out extensive drilling of plaster after flaming the surface. In no plaster sample did we obtain tetanus spores, except where aerial dust contamination was certain.

Tetanus spores were found widely distributed throughout the theatre block: from all floors of the theatres, the anæsthetic room, the main corridor, sluice and the surgeons' changing room. *Cl. tetani* was also isolated from the broken plaster in the wall of the annexe corridor, the wall of the anæsthetic room, the light over Theatre 1 operating table and the light bulb in the packing room.

Positive findings were also obtained from points in the ventilation system of Theatres 1 and 2 as well as from the outside roof adjacent to the ventilation exhaust. No spores were found in the nurses' annexe.

Undoubtedly the vigorous cleaning efforts, which had been put in hand when the theatres were closed, had contributed to the wide dissemination; but it is worth noting that spores were found readily despite these decontamination processes.

A search was also made for possible vehicles of infection.

Some 160 gloves were examined from 10 drums by swabbing, with a moistened swab, the dorsum, palm and webs of each glove, *Cl. tetani* was isolated from six individual gloves comprising sizes 6, 6½, 7 and 7½ in five drums. Spores were also found in the size 7½ of a series of glove sorting and storage cardboard boxes kept in a cupboard on the wall of the packing room in the surgeons' annexe.

Dressings and gown drums were sterilized in one autoclave while the glove drums were treated in a separate instrument. In this they were kept in the chamber for 30 minutes in a vacuum of about 12 in. mercury while steam pressure was built up to 30 lb./sq. in. in the autoclave jacket. It was estimated that the drums were held in hot air at about 125° C. for half an hour.

As all catgut proved sterile and no instruments, dressings or powders were shown to contain tetanus spores it was presumed, through the association of *Cl. tetani* with the gloves, and their method of sterilization, that the gloves were the vehicle of infection.

Although there had been ample opportunity for the gloves to become contaminated with tetanus spores it was not easy to see what had caused the precise timing, as the methods of packing and sterilization had been in use for a considerable time without a like catastrophe occurring.

On the timing of the outbreak three possibilities presented:

The first of these I have already touched on. The presence of animal hair in the wall plaster, taken in conjunction with Sevitt's positive findings, suggested that, when the Theatre 1 ceiling had been repaired in the winter, some

heavily contaminated material had been freed into the theatre ventilation system. Dr. Knappett's extensive work, however, combined with the fact that the repairs had been completed by January 10 appeared to rule out this possibility.

The second theory requiring consideration arose from an extensive arm injury sustained by a man at work on February 8. He received 3,000 units ATS on admission to hospital. His arm became heavily infected under his immobilization plaster, and the foul plaster and dressing were removed in Theatre 2 on February 19. No swab was taken. Two days later the first tetanus victim was infected. From a study of the routine involved in the theatres, and with due regard to the volume of work accomplished, it appeared that the turn-round of the gloves from the time of one use to the next, after sterilization, was usually just two days. Coincidence seemed perfect, but proof was unobtainable. The patient's arm had been amputated (and immediately destroyed) on the day the theatres closed. The stump had healed by March 8 and an attempt to demonstrate an abnormally high antitoxin level in the man's serum proved fruitless (the level was less than 0·001 units/ml.).

Whether the dressing and plaster of a lesion such as this patient's, heavily infected with putrefactive organisms, and moist and warm as it was, could support the growth of *Cl. tetani* without penetration of toxin to the patient is a subject for speculation and the chain of circumstance, linking this injury with the flood of tetanus spores in the theatre, is incomplete.

There is yet one other possibility which presented, but, as it was not until later that evidence was forthcoming to lend it some credence, I have left it till last.

Arising indirectly from this enquiry into the Stoke outbreak the Public Health Laboratory Service completed a survey of the incidence of tetanus spores in material associated with wound dressings. The result of the survey is about to be published so I shall not anticipate it more than to observe that tetanus spores are frequently present in unbleached "grey" cotton-wool, and in orthopædic cotton-wool bandages. The degree of contamination must and does vary considerably, probably depending more upon the local conditions of cultivation and harvesting of the cotton than upon any other factors.

It is perhaps possible for a heavily infected roll of unbleached cotton-wool, torn asunder in the theatre precincts, to disseminate tetanus spores into the theatre atmosphere. However, further evidence will be presented elsewhere which appears to contradict this hypothesis. At any rate, it would appear that this system did not operate at Stoke and the weight of evidence lies in favour of the infected arm as being the source of the theatre contamination.

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Tetanus in the Civilian Population of England and Wales

Tetanus is not a notifiable disease in this country and almost the only figures available are those of mortality. The figures now presented are mainly an extension over a further ten-year period of some already published (Conybeare and Logan, 1951).

Fig. 1 shows the course of the crude annual

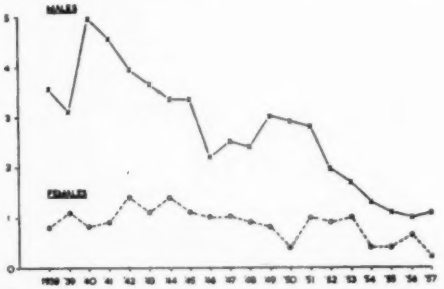

FIG. 1.—Tetanus: death-rates per million living 1938–1957.

death-rate from tetanus per million living of the two sexes in England and Wales during the twenty years 1938–57. Apart from the war years the tendency has been for the male rate to decline so that in 1957 it was about one-third what it was in 1938. For females the rate has not declined so much as for males. The preponderance of male over female deaths in 1957 was less than it was in 1938 but the male/female ratio is still of the order of 3/1. In absolute figures the rates mean 23 male deaths and 5 female deaths in 1957 as against 72 male deaths and 17 female deaths in 1938.

Fig. 2 sets out by age and sex the mean annual death-rates over the two ten-year periods 1938–47 and 1948–57. The characteristic age pattern of tetanus deaths is seen in the male chart for 1938–47. This pattern is repeated but at a lower level in the male chart for 1948–57. The female chart shows a similar repetition of the age pattern at a lower level up to the age of about 35. After that age the rates for 1948–57

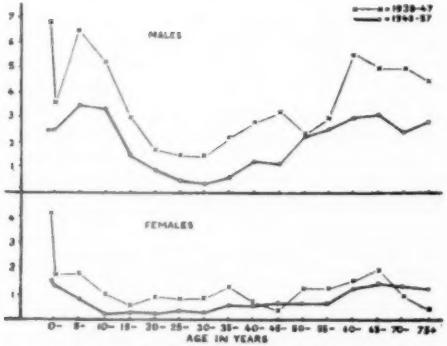

FIG. 2.—Tetanus: death-rates per million 1938–1947 and 1948–1957.

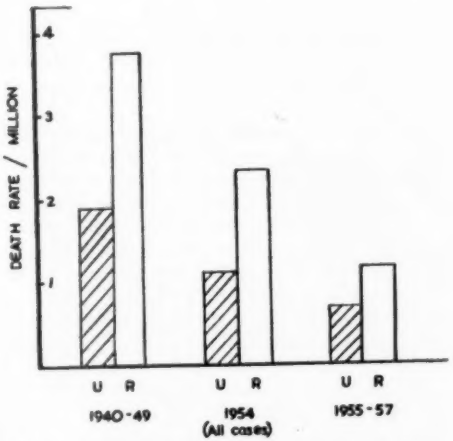

FIG. 3.—Tetanus: Urban (U) and rural (R) death-rates 1940–1957.

are not always lower than they were in the previous decade.

A difficulty associated with these figures arises from the International System of Classification at present in use for the assignment of causes of death. This requires that deaths from tetanus are assigned to it (No. 061 in the I.S.C.) except when the tetanus has arisen from an injury which is more than very slight; the death must then be assigned to the injury.

A special examination was carried out by the Registrar-General in 1954 on all death certificates mentioning tetanus in that year to determine the extent to which some were being lost from the statistics by assignment elsewhere. 61 certificates were traced of which only 37 had been assigned to tetanus and the remaining 24 to other causes. A scrutiny of the causes in the two series suggested (Registrar-General, 1954) that there was on the whole little difference between them, and that the existing international procedure whereby they were assigned in different ways had resulted simply in reducing the apparent total of deaths by 39% with, probably, very little overall statistical advantage.

Apart from the well-defined male preponderance there is in the tetanus death figures for England and Wales a well-marked urban/rural differential. It has been shown (Conybeare and Logan, 1951) that between 1946 and 1948 in both sexes death-rates in rural districts were about three times as high as in Greater London and the large towns and more than half as high again as in the smaller towns. Fig. 3 shows the persistence of the urban/rural differential since 1948 although the rates have fallen.

Morbidity.—There are no readily available figures for the morbidity due to tetanus in this country. By assuming a case fatality rate of from 25 to 50% it may be estimated that the annual morbidity now ranges from about 50 to 150 cases per annum. It is possible to use the Hospital In-Patient Enquiry to check on this estimate; this is a sampling investigation in which about one in ten of the annual discharges (including deaths) from the hospitals of this country are analysed regarding the disease for which treatment was given. From this analysis an estimate of the annual incidence of given diseases in the hospital population can be obtained. The accuracy of this estimate varies according to the frequency with which the particular disease concerned appears in the sample. In the case of tetanus this frequency is very low and the estimate is therefore inaccurate. Table I shows

TABLE I.—HOSPITAL IN-PATIENT ENQUIRY 1953–1956

Year	1953	1954	1955	1956
Cases in sample ..	8	6	4	16
Estimated Total ..	398	219	104	240
Cert. deaths	61	37	33	37
Cases fatal % ..	15	15	32	16

estimates which have been made on this admittedly crude basis of the hospital discharges from tetanus in the years 1953–1956. The estimated total of hospital-treated cases in these four years ranges from 104–398. The total of 104 for 1955 seems inconsistent with figures for 1954 and 1956 which are more than twice as great although the death totals in all these three years were approximately the same.

PREVENTION

Undoubtedly the civilian morbidity and mortality from tetanus in this country is now considerably lower than in most other European countries (World Health Organization, 1955) but

it is not as low as in most parts of the United States (Axnick and Alexander, 1957). The methods at present being used in this country to *prevent* this disease among civilians are as follows:

(1) *Urgent immunization necessitated by injury.*—For this purpose in civilian practice we continue to rely on passive immunization with anti-tetanus serum. It seems probable that from 1 in 5 to 1 in 15 of all patients referred to hospital casualty departments in this country receive injections of this serum (Moynihan, 1955). This means something of the order of 750,000 to a million such injections per annum. Unpleasant reactions indicative of sensitization probably occur in about 5% of those inoculated, i.e. in about 50,000 cases per annum. Most of these reactions are of the delayed "serum sickness" type which are to some extent controllable by anti-histaminic drugs but, nevertheless, they are in some cases still the cause of disabling sequelæ. A few of these reactions are "anaphylactic" and therefore dangerous. The Registrar-General's figures show that between 1945 and 1957 a total of 16 deaths was attributed to the injection of anti-tetanus serum. 10 of the deaths were in males, 6 in females. Deaths from this cause seem to be increasing and most of them have occurred in the 10 to 30-year-old age groups.

(2) *Routine immunization (i.e. not immediately necessitated by injury).*—The prophylactic used for this purpose is tetanus toxoid given either alone or in combination with other antigens, such as diphtheria toxoid and pertussis vaccines. At present it is permissive but not obligatory on Local Health Authorities in England and Wales to formulate schemes for immunization against tetanus under Part III of the National Health Service Act, 1956. So far only 38 out of a total of 146 Local Health Authorities have sought the Minister's consent to the provision of such immunization in their own areas. The total number of children being immunized under these schemes is at present unknown because there is, so far, no official requirement regarding records and annual or other returns. In most, if not all, of these schemes combined antigens are used. These are obtained by the Local Health Authorities direct from the manufacturers, and are not purchased centrally by the Ministry and distributed as a free issue, as has been the practice with smallpox vaccine, diphtheria prophylactics and poliomyelitis vaccine.

In addition to these Local Health Authority schemes there is undoubtedly a certain amount of routine immunization using tetanus toxoid (either alone or in combination) which is undertaken independently by general practitioners who can prescribe such antigens for use in registered patients on Form E.C.10. The amount of immunization done in this way is also unknown but it is probably not very large. There is also the contribution, unknown in degree but possibly substantial, which has been made to the prevention of civilian tetanus among adults of the younger age groups by the routine active immunization carried out in the armed forces during the last war.

The most important question in connexion with prevention is whether it is practicable to increase the routine and urgent use of tetanus toxoid (which is a very trouble-free prophylactic) to an extent sufficient to initiate and maintain among civilians a degree of immunity which would diminish or even eradicate the present morbidity and mortality from tetanus.

If, as a consequence of an increased use of toxoid, it became possible to abandon the current practice of giving anti-tetanus serum in the urgent immunization necessitated by injury the gain would obviously be very great indeed. The chief practical difficulties seem to be:

(*a*) To obtain sufficiently high and sufficiently uniform acceptance rates in a civilian population among whom *all* immunization is done on a *voluntary* basis. The locally variable acceptance rates hitherto obtained in other forms of immunization practised in this country hardly ever exceed 75% and are probably inadequate.

(*b*) To devise a foolproof means of identifying the person who has been actively immunized and therefore should receive toxoid rather than anti-tetanus serum urgently when injured.

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Proceedings of the Royal Society of Medicine Vol. 52 115

Section of Odontology

President—W. G. SENIOR, C.B.E., Ph.D., F.D.S.

Meeting
November 24, 1958

Two Specimens Illustrating Proteolysis of Dentine

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Case I.—A man of 21 (Professor W. E. Herbert's patient), attending on account of dental pain, was found to have a chronically infected first lower premolar, the bone about which had been almost completely lost. Radiographs showed that the pulp cavities of many teeth were larger than normal and that the dentine cast an irregular shadow (Fig. 1). The premolar was extracted and examined microscopically after decalcification. It showed an extreme degree of defective calcification of rachitic type (Fig. 2) but a normal tubular pattern. Subsequent enquiry revealed the patient had been investigated ten years ago by Dr. W. Sheldon, to whom I am indebted for information. He was thought to have vitamin-resistant rickets. In the sections the most striking feature was that in most of the interglobular areas no collagenous matrix remained (Fig. 3). The pulp cavity contained only bacterial growths, pus, and at one apex chronically inflamed pulp tissue, the surface of which had become epithelialized. There was an abnormal connexion between the pulp cavity and the periodontal membrane, through which epithelium could well have migrated to this site.

FIG. 1 (*Case I*).—Radiograph of some of the lower teeth.

FIG. 2 (*Case I*).—Lower premolar showing very imperfect calcification and large pulp cavity. Hæmatoxylin and eosin. ×3.

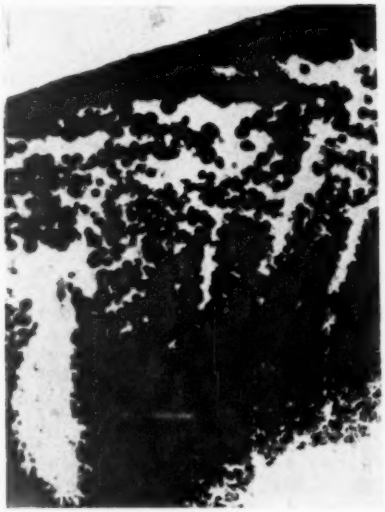

FIG. 3 (*Case I*).—Part of the coronal dentine showing large interglobular areas which contain no collagenous matrix. The pulp cavity is at bottom right. Van Gieson. ×33.

It is clear that the absence of collagenous matrix in the interglobular areas is not a malformation but the result of bacterial invasion. The pattern of calcification of the dentine is such as could only have occurred in a normal matrix; some interglobular areas contain collagenous matrix; others contain matrix which is partly destroyed and occupied by bacterial growths (Fig. 4). In all areas the dentine which had been calcified was not affected, so that calcospherites remained isolated, and in only a few areas have the bacteria entered the dentinal tubules to any extent. There is evidence in some interglobular spaces that some components of the tubular walls have been selectively spared, so that the tubules can be traced across the matrix-less space, looking rather like the strings of a harp (Fig. 5). It is interesting to note that the enamel of this man's teeth appeared approximately normal clinically.

Discussion.—It is common in teeth, the pulps of which have been infected and destroyed, to find that the predentine has disappeared and that calcospherites remain isolated but intact at the surface of the calcified dentine. This is ascribable to the action of proteolytic bacterial enzymes, to which the matrix of calcified dentine is not accessible or available. The present case must be interpreted as an extension of this process, made possible by the great porosity of the dentine which has allowed bacteria and their enzymes to spread widely through almost its whole extent. The selectivity of this proteolysis is shown not only by the integrity of the matrix of even the smallest calcospherites but also in some areas by the preservation of components of the tubular walls.

FIG. 5 (*Case I*).—Dentine showing that in some interglobular areas parts of the walls of the dentinal tubules remain extending like strings across the spaces. Three areas from above downwards show increasing degrees of dissolution. Van Gieson. ×300.

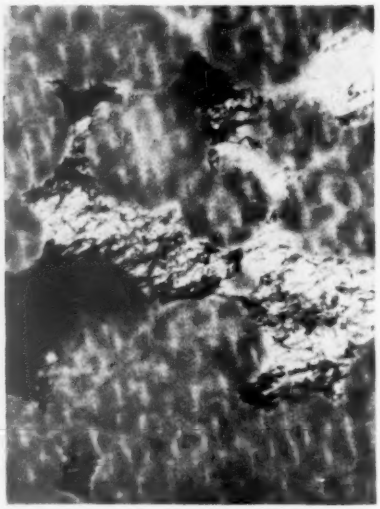

FIG. 4 (*Case I*).—Small interglobular areas containing bacterial growths which show a tendency to extend parallel to incremental laminations. Only a few tubules have been invaded by bacteria. Gram's stain. ×330.

Case II.—In contrast with the preceding case is another in which bacterial enzymes appear selectively to have spared the matrix of the interglobular spaces, while degrading that which had been calcified. The specimen is a molar tooth from a woman of 69 suffering from Paget's disease, in which there is a small carious cavity involving the dentine at the side of a cusp. The shallow cavity contains, besides bacteria, some fragments of altered enamel, which in turn are partly covered by calculus extending from the neck of the tooth (Fig. 6). A band of dentine surrounding the cavity no longer stains red with van Gieson's stain, indicating that the collagen has been degraded (Fig. 7). On the margin of this zone adjoining the more normal matrix it is evident that the matrix of the interglobular spaces has resisted degradation more than the calcified matrix. The same is true of the collagen immediately surrounding some of the tubules

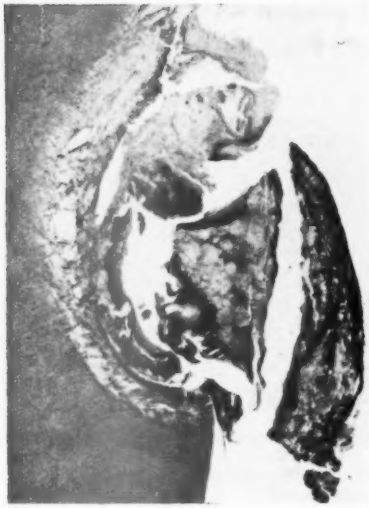

FIG. 6 (*Case II*).—Carious cavity containing bacterial growths and enamel matrix partly covered by calculus. Hæmatoxylin and eosin. ×53.

FIG. 7 (*Case II*).—At the deeper part of the carious area the interglobular pattern is revealed, the interglobular matrix continuing to stain red while the once calcified matrix does not. Van Gieson. ×95.

FIG. 8 (*Case II*).—Enlarged view showing the preferential degradation of the matrix in areas which once were calcified. The walls of isolated tubules like the interglobular matrix show some resistance to degradation. Van Gieson. ×315.

(Fig. 8). There is comparatively little bacterial occupation of the dentine, only a small proportion of tubules containing organisms and few Gram-positive.

Discussion.—These findings differ from those in the previous case and possibly from ordinary caries in showing some degree of selective preservation of the matrix of the interglobular areas with respect to the dentine that has been fully calcified. It is also noteworthy that while proteolysis in the first case has led to complete dissolution of the collagenous matrix, in the second the once calcified matrix, though it has completely lost its property of staining red with van Gieson's stain, still maintains its general form and some elements of its structure.

This specimen may show a form of arrested or very slow caries, in which bacterial invasion is inconspicuous but in which some form of slow degradation of protein is possibly still occurring through the diffusion of active substances.

To summarize, two specimens are described. In the first the matrix of the interglobular dentine had been selectively destroyed; in the second it had been selectively spared.

Acknowledgments.—I am greatly obliged to Mr. J. E. Hutchinson for making the histological preparation and photomicrographs.

The Pattern of Mineralization of Human Dental Enamel

By H. S. M. Crabb, M.D.S., F.D.S. R.C.S.

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Two principal theories about the pattern of enamel mineralization have been advanced in the first half of this century, namely, the theory of von Ebner (1906) and Chase (1929, 1932, 1935) and the theory of Diamond and Weinmann (1940). The incremental pattern of matrix deposition was established by Schour and Massler (1936), Schour and Kronfeld (1938), and Schour and Hoffmann (1939). Most of the conclusions of von Ebner (1906) and Chase (1929, 1932, 1935) were based on staining reactions in sections of decalcified developing teeth while those of Diamond and Weinmann (1940) were based on the loss of organic matrix in similar sections. There appears, however, to be no satisfactory evidence to support a relationship between affinity for stain or the loss of organic matrix and the amount of calcium salts present in the enamel. A direct assessment of mineralization may be made by use of the techniques of microradiography and the measurement of intrinsic birefringence in polarized light. Work on developing enamel based on the use of one or both of these techniques is included in reports by Schmidt (1923–25, quoted by Harders-Steinhäuser), Harders-Steinhäuser (1938*a*, *b*), Glock *et al.* (1942), Applebaum (1943), Hals (1953), Engfeldt *et al.* (1954), Engfeldt and Hammarlund-Essler (1956), Crabb and Darling (1956, 1958) and Allan (1957, 1958).

This report is concerned with the results of the study of ground sections of the enamel of developing teeth by microradiography, the assessment of intrinsic birefringence and the examination of stained decalcified sections.

130 ground sections were made of developing teeth ranging from those obtained from a fœtus of 32 weeks' maturity to those from a boy of 7 years. Longitudinal buccolingual and transverse sections were prepared and microradiographed by the technique described by Darling and Crabb (1956), with the one exception that a polyester resin was used in place of methyl-methacrylate for the embedding of some specimens. The microradiographs were then examined for the broad pattern of mineralization and the detail of the stages by which the pattern is built up in relation to the fine structure of the enamel.

The earliest stage which was observed was found in the deciduous canines at birth. At this stage only one-third to one-half of the eventual crown form has been laid down, yet the enamel next to the amelodentinal junction shows a band of high radiopacity, indicating a degree of mineralization considerably in advance of the mineralization of the rest of the matrix. This highly mineralized zone at the amelodentinal junction appears soon after the matrix is laid down. It is seen to be present in all recently formed enamel such as the growing cervical margin and the thin occlusal part of the developing enamel joining the cusps in molars (Figs. 1A, B).

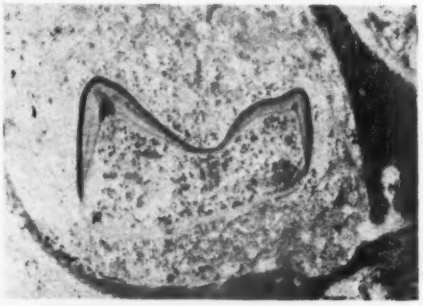

Fig. 1A.—Ground section of a lower deciduous first molar from a full-term fœtus. Buccolingual section seen by transmitted light. ×7·5.

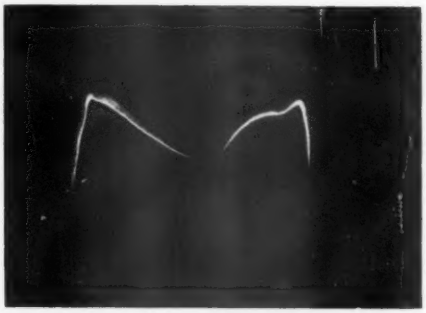

Fig. 1B.—Microradiograph of the ground section shown in Fig. 1A. ×7·5.

In the next stage the zone of high mineralization spreads out towards the outer border of the tip or cusp of the tooth (Fig. 2). At the same time this zone spreads out from the amelodentinal junction along the whole length of the enamel. This occurs both labially and lingually and, in the molars, across the occlusal enamel as well. The direction of spread is irregular and the border of the zone appears in some places to be parallel to the amelodentinal junction and in others parallel to the enamel surface.

FIG. 2.—Microradiograph of a ground section of a lower deciduous second molar from a full-term fœtus. The mesial buccal cusp is shown. The radiopaque zone occupies the greater part of the enamel over the cusp and extends along the amelodentinal junction. ×50.

FIG. 3.—Microradiograph of a ground section of a lower deciduous central incisor from a full-term fœtus. The distribution of the highly radiopaque zone indicates that mineralization of the lingual enamel is in advance of the labial enamel. ×8·5.

FIG. 4.—Microradiograph showing part of the labial enamel of an upper deciduous central incisor from a full-term fœtus. The thin zone of radiopacity at the enamel surface is demonstrated, together with the zone of radiolucency immediately beneath it. ×75.

In upper and lower incisors and canines the lingual enamel appears to mineralize before the labial enamel (Fig. 3), and this is seen in both longitudinal and transverse sections, confirming the findings of Engfeldt and Hammarlund-Essler (1956). There was no indication that mineralization occurred earlier in one molar cusp than in the others as far as could be judged from buccolingual sections.

In some fœtal and postnatal teeth there is a thin band at the enamel surface which shows greater radiopacity than the enamel immediately underlying it (Fig. 4). The thickness of this highly mineralized band at the enamel surface is approximately 5 microns and the underlying band of lower mineralization is approximately 10 microns wide. This surface zone could not be correlated with any particular stage of development but it is obvious that it occurs after the completion of the full width of the matrix. The occurrence of this zone has also been reported by Engfeldt and Hammarlund-Essler (1956).

In microradiographs of postnatal material radiopaque and radiolucent bands lying parallel to the striæ of Retzius and external to the neonatal line are seen in the mineralizing matrix of the enamel. These conform to the incremental pattern for the deposition of the matrix as described by Schour and Massler (1936), Schour and Kronfeld (1938) and Schour and Hoffmann (1939). In fœtal material such lines appear to be the exception and when present are poorly marked. This agrees with the observations of Rushton (1933, 1939) that structural defects are more common in postnatal than in prenatal enamel.

Alternately radiopaque and radiolucent bands running parallel to the striæ of Retzius have also been seen in a zone approximately 50 microns wide confined to the outer border of the enamel in the cervical half of the unerupted central and lateral permanent incisors of a girl aged 5 (Fig. 5). Similar appearances were

FIG. 5.—Microradiograph of a longitudinal ground section of an unerupted $\underline{|2}$ from a girl aged 5, showing a striated zone at the surface of the labial enamel. ×75.

found in the cervical third of the enamel of a lower second premolar which was contained in a dentigerous cyst. It is not known whether these appearances represent a stage of normal development of the enamel, for fault lines and surface pits were seen in the ground sections of these teeth indicating that they were hypoplastic.

In the matrix which is only partly mineralized, as distinct from the zone of high mineralization which is moving out from the amelodentinal junction, alternately radiopaque and radiolucent lines are seen running parallel to the direction of the prisms (Fig. 6). These lines occur at intervals of approximately 6 to 8 microns, similar to the width of the prisms, and are therefore likely to

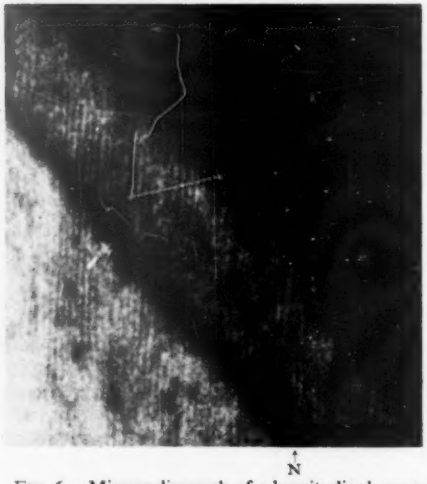

FIG. 6.—Microradiograph of a longitudinal ground section of an upper central incisor from an infant of 10 weeks. Radiopaque and radiolucent lines, which are running parallel to the prisms, are demonstrated. The neonatal line (N) is relatively radiolucent. ×220.

be related to prism structure. From such sections cut parallel to the long axis of the prisms, however, it is difficult to say which parts of the structure these lines represent, but there appears to be an initial preferential mineralization of one part of the structure. To elucidate this point sections were cut transversely to the long axis of the prisms. Where the prisms have been cut transversely the radiopaque areas appear in the centre of a honeycomb pattern of radiolucent structure (Fig. 7). It appears therefore that the centre of the prism is mineralized first. In microradiographs of longitudinal sections the radiopaque lines which run parallel to the prisms are wider than the radiolucent lines in the enamel near the amelodentinal junction but nearer the enamel surface the radiolucent lines are wider than the radiopaque lines. This suggests that the process of mineralization moves out from the centre of the prisms as it spreads out from the amelodentinal junction to the enamel surface. Further evidence is needed before the present findings can be fully interpreted.

The basic pattern of mineralization, as demonstrated by microradiographs, consists of two stages. There is first a deposition of matrix in increments delineated by the striæ of Retzius. This matrix may exist for a very short while in a wholly organic state but is soon partly mineralized. This is the primary phase. This is shortly followed by a phase of higher mineralization, the

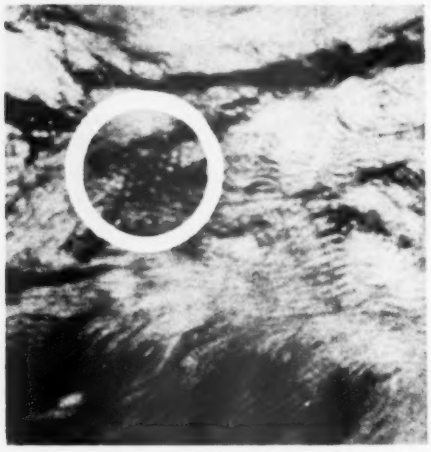

FIG. 7.—Microradiograph of a ground section of a deciduous second upper molar from an infant of 44 weeks. A group of prisms (within circle) has been cut transversely. ×220.

secondary phase, which starts from the whole length of the existing amelodentinal junction and moves outwards towards the enamel surface (Fig. 8). The time interval between the start of the primary and secondary phases appears to be small. The secondary phase has started long before all the tooth form is laid down, so that the two phases are occurring simultaneously for the greater part of the mineralization process. The secondary phase starts to move out from the amelodentinal junction in the incisal or cuspal region of the tooth. The advancing edge of this phase is at first approximately parallel to the amelodentinal junction and later, as the outer border of the enamel is approached, it becomes parallel to the enamel surface. This pattern of

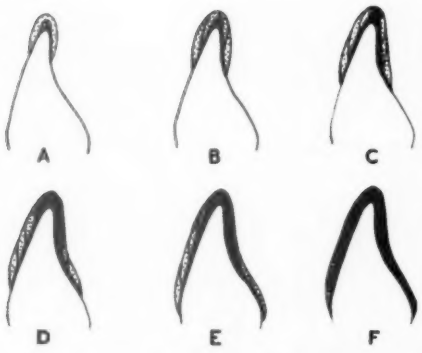

FIG. 8.—Diagram to illustrate the stages (A–F) in the pattern of mineralization of an incisor tooth. Continuous lines represent incremental striæ. The stippled zone is partly mineralized (=primary phase). The heavily shaded zone indicates the spread of final mineralization (=secondary phase).

mineralization is fundamentally different from that proposed by Diamond and Weinmann (1940), but is in general agreement with that deduced by Darling (1956*a*) to explain the occurrence of zones of enamel hypocalcification in amelogenesis imperfecta.

In order to confirm the findings from microradiography and to obtain some measurements of the gradient of mineralization from the amelodentinal junction to the enamel surface, the intrinsic birefringence of enamel in ground sections of developing teeth was measured. For practical purposes it may be assumed that the intrinsic birefringence gives an indication of the degree of mineralization. Sections were imbibed with Thoulet's solution (R.I. 1·62) as described by Darling (1956*b*) and the birefringence measured by means of a Berek compensator. A microradiograph of a deciduous incisor from an infant of less than 1 week is shown in Fig. 9, and Fig. 10 indicates the measurements of intrinsic birefringence obtained along the survey path A–A′ (labial enamel) and B–B′ (lingual enamel) marked on Fig. 9. It is seen that the negative intrinsic birefringence of the lingual enamel is greater than that of the labial enamel. In both labial and lingual enamel the birefringence diminishes from the amelodentinal junction to the enamel surface, confirming the pattern of mineralization demonstrated in the microradiographs.

Stained sections of decalcified developing teeth have been compared with microradiographs of ground sections of contralateral teeth. There was no evidence of matrix solubility which could be correlated with the pattern of mineralization derived from the microradiographs. In many sections there was a space between the matrix and the amelodentinal junction and it might be possible to argue that some solubility of matrix had occurred in this region. But in some sections the complete enamel matrix remained attached in places to the dentine while the corresponding microradiograph of the ground section of the contralateral tooth indicated a high degree of

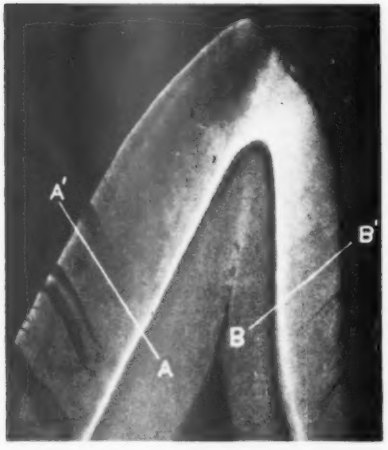

FIG. 9.—Microradiograph of a ground section of a deciduous upper central incisor from an infant of less than one week. A–A′ and B–B′ indicate the survey lines of labial and lingual enamel respectively for the assessment of birefringence. ×37.

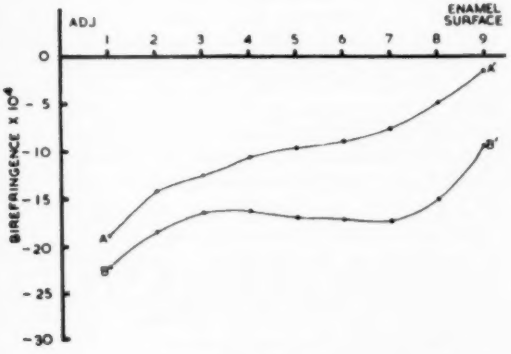

FIG. 10.—Graph relating intrinsic birefringence to points within the enamel corresponding to survey lines shown in the microradiograph (Fig. 9).

mineralization in the enamel next to the amelodentinal junction. This is demonstrated in Figs. 11 and 12. Where a space exists in the decalcified section between the matrix and the dentine it seems likely that the matrix has become detached from the amelodentinal junction. It is quite evident that the loss of matrix in decalcified sections cannot provide an indication of the pattern of mineralization. Allan (1957, 1958) concurs with this. This means that the conclusions of Diamond and Weinmann (1940) which are based on the loss of organic matrix cannot be considered valid, for they equated the pattern of loss of matrix in decalcified sections with the pattern of mineralization of the enamel.

FIG. 11.—Microradiograph of a ground section of a lower right deciduous central incisor from a full-term fœtus. ×12·5.

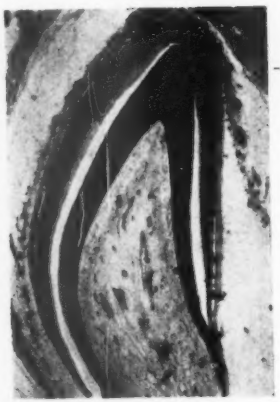

FIG. 12.—Decalcified section of the contralateral tooth to that shown in Fig. 11. Stained with Mallory's aniline blue-orange G. The complete matrix is attached to the dentine at A, corresponding to the zone of high mineralization in Fig. 11. ×12·5.

To summarize: The pattern of mineralization of enamel which has been demonstrated shows that the matrix is formed in increments, delineated by the striæ of Retzius, the matrix rapidly undergoing partial mineralization. This constitutes the primary phase of mineralization. This is shortly followed by the secondary phase which spreads outwards from the amelodentinal junction to the enamel surface, with its advancing front at first parallel to the amelodentinal junction and later to the enamel surface. The two phases take place simultaneously for the greater part of the time of enamel mineralization. The outer border of the enamel appears to mineralize before the zone immediately underlying it. In incisors and canines the lingual enamel mineralizes before the labial enamel. In the primary phase of mineralization there appears to be a preferential mineralization of the prism core, so that mineralization spreads out from the centre of the prism. It has been demonstrated that the pattern of loss of organic matrix in decalcified sections is no guide to the pattern of mineralization.

Acknowledgments.—I should like to thank Professor A. I. Darling for his interest and encouragement. I also wish to thank Dr. M. V. Stack, of the Medical Research Council External Staff, University of Bristol, and Dr. N. J. Brown, Consultant Pathologist, Southmead Hospital, Bristol, for providing me with most of the fœtal material, Mr. B. G. H. Levers and Miss B. Fifield for technical assistance, and Mr. F. G. Godman, University of Bristol Photographic Department, for the reproduction of the diagrams.

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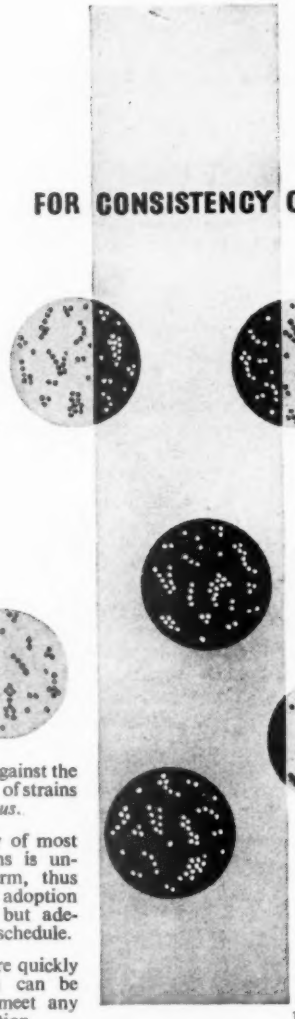

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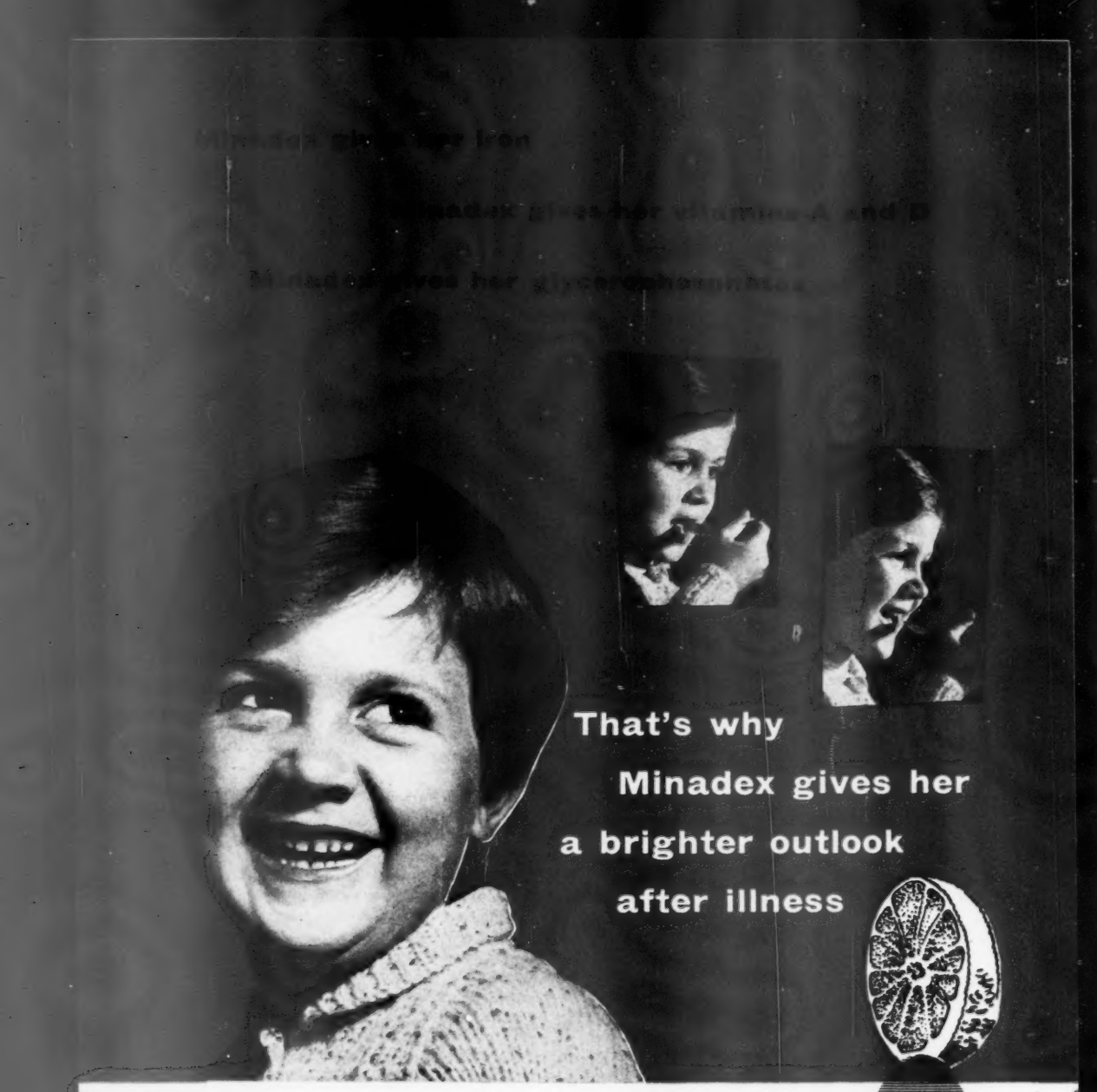

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Meeting
November 5, 1958

The Last Illness of Oscar Wilde

By TERENCE CAWTHORNE, F.R.C.S.

London

AT ten minutes to two on the afternoon of November 30, 1900, there died in Paris a man so famous, or perhaps I should say infamous, that his assumed name of Sebastian Melmoth concealed from but few the fact that he was Oscar Wilde.

Having achieved fame, popularity and success as a poet, a playwright and a wit, he became notorious as a profligate and a homosexual, was shunned and scorned as a convicted felon; finally to be fortified by the Rites of the Holy Catholic Church into which he was received but two days before he died.

The certified cause of death was cerebral meningitis and almost all who knew him felt that his mode of living contributed towards his death at the early age of 46. With the exception of Frank Harris, none of his biographers who have dealt with the cause of his death have doubted that neurosyphilis was responsible for his terminal illness and that persistent alcoholic excess hastened his end.

This I do not believe, because, without wishing in any way to condone or deny his habits, I think that a careful study of his life and of his last illness must lead to the conclusion that he died of nothing less than an intracranial complication of suppurative otitis media. Such a disaster, for disaster it was in the days before antibiotics and modern surgery, can occur at any age, often to those who have led blameless lives. Nobody could say that Oscar Wilde led a blameless life; but regular indulgence in the accepted pleasures, as well as in some of the less acceptable vices, of life, does not close the door to other causes of death. In those days the part played by chronic ear disease in the causation of terminal intracranial infection was rarely appreciated; so it is not surprising that his death was attributed to his folly and self-indulgence which were obvious, rather than to an obscure ear infection which he himself had always concealed.

But, if our opinion of his terminal illness is to be something more than casual surmise, it will be advisable to enquire into his family and into his past history as well as into the events which led to his death.

He was born in Dublin in 1854, the second son and child of Sir William and Lady Wilde and was given the names Oscar Fingall O'Flahertie Wills Wilde. Some thirty years later when speaking of his name he said: "My name has two O's, two F's and two W's." He added: "A name which is destined to be in everybody's mouth must not be too long; besides it comes so expensive in the advertisements."

These extraordinary names were not surprising as they were given him by unusual parents. His father was the leading oculist and aurist of the day. He also had an international reputation as an archæologist, and received his Knighthood in 1864 for his services in connexion with the Irish census. A small man of great energy and drive, he suffered from asthma and, despite his appearance and general behaviour, was attractive to and attracted by women. In fact, a serious scandal with one of his female patients ended in a libel suit and his social and professional eclipse.

Oscar's mother wrote patriotic verse and pamphlets under the name of "Speranza". Besides being a poetess and an ardent Irish Nationalist, she was a poseuse. She was tall, rather heavily built and, for those days, heavily made up. She was certainly an unusual woman who not only treated her second son Oscar as a girl, which she had so fondly hoped for, but also dressed him as a girl during his early years. It has been suggested that this was the basis for his sexual inversion.

A daughter, Isola, was born in 1857 and died, of what is not recorded, ten years later. She was a family favourite and Oscar wrote of her in one of his earlier poems:

> "Tread lightly, she is near,
> Speak gently, she can hear
> The daisies grow."

Sir William Wilde died in 1876 at the age of 61 and Lady Wilde in 1896 at the age of 70, while Oscar's brother, Willie, older by two years, predeceased him by a year.

Trained as a barrister, Willie became a journalist and is said to have drunk himself into an early death. The two brothers had little in common and Willie as the elder could never accept his younger brother's fame and success in face of his failure to make a name for himself.

Dr. Macdonald Critchley in a medical appreciation of Oscar Wilde mentions that Willie was known by the contemptuous nickname of "Wuffalo Will"; this was no doubt inspired by his lack of success as the second husband of a rich American widow. Their marriage did not last long as she expected her new husband to manage the family business, but Willie's idea was to make the business work for him.

When Oscar was released on bail after his first trial he was refused entry to every hotel, thanks to the activity of the Marquess of Queensberry, and so, late at night, in a state of physical and emotional exhaustion, he sought refuge in his mother's home in Oakley Street, Chelsea. Willie let him in and, relating the experience not without relish to his friends afterwards, in a remarkable mixture of metaphors which perhaps indicates his muddled ways, Willie said: "Oscar came tapping with his beak against the window pane and fell down on my threshold like a wounded stag."

The Wildes were not a long-lived family, but apart from Sir William's asthma and a tendency on the part of all the male members of the family to drink too much there is nothing of any great significance in the family history.

Oscar grew up to be tall and, though heavily built, seems to have been remarkably healthy. He was indolent and disliked all forms of physical exercise, declaring that he neither liked to kick or be kicked. Though large and on the fat side and avoiding all forms of athletics and most athletes, he was powerful enough and never ran away from any form of trouble either then or later. One night the Junior Common Room at Magdalen decided to raid Oscar and smash up his rooms, including the famous "blue china". The first three or four members of the advance party were thrown downstairs by Wilde and he carried the fourth, who was also the ringleader, down to his own rooms and buried him underneath his own furniture, then inviting the onlookers to join in drinking the ringleader's health in his own wine.

Throughout his adult life he over-ate, over-drank, and persistently refused to take exercise. His capacity for alcohol was legendary, and on many occasions saw under the table those who had set out to make him drunk. He had a pose of being idle but in reality he must have been a hard and a quick worker, for he produced a lot in the twenty-odd years of his working life. What he disliked was any form of routine and set hours of work; but he was undoubtedly capable of hard and effective work for short periods. He is said to have finished his greatest play, possibly the greatest drawing-room comedy ever written, "The Importance of Being Earnest", in three weeks.

He always admired youth, beauty and health and at the same time had an almost morbid dislike of age, ugliness and disease; so it is not surprising that nowhere except in "De Profundis" and at the very end of his life do we hear anything from him about personal illness. You will recall that in "De Profundis", a long letter written while in prison to Lord Alfred Douglas, he described how, when they were staying in Brighton, he nursed Douglas through an attack of influenza; and how when he caught it, Douglas neglected him.

It is generally believed that he contracted syphilis while an undergraduate at Oxford, and the bad state of his teeth has been attributed to the mercury which is said to have resulted in a cure.

Robert Sherard refused to believe that the crime for which Oscar Wilde was convicted was committed consciously and he attributed it to an epileptic state brought about by over-indulgence in food and drink. Sherard was a simple but loyal soul who refused to believe ill of his friend, though his explanation must appear to most as a piece of special pleading. Bernard Shaw quotes Oscar as having written to Sherard from prison advising him "Don't fight more than six duels a week".

The first record of any ear trouble comes from Lord Alfred Douglas who, when visiting Wilde in the public interview room in Holloway Gaol in April 1895, where he was awaiting trial on a charge of homosexuality, wrote "Poor Oscar was rather deaf. He could hardly hear what I said in the Babel". This certainly was not otosclerosis; it could have been nerve deafness and of course syphilis inevitably comes to mind as the cause. It could, however, have been any form of unilateral deafness such as might happen with chronic suppurative otitis media.

Some months later in Wandsworth Prison, before he was transferred to Reading, Wilde was taken ill with giddiness, sickness and earache.

He was forced out of bed to attend Chapel. He fell down, and his ear bled and discharged at least for months afterwards.

As this is the first mention of any infective ear disease it will be as well to report Frank Harris' account of what Oscar Wilde told him about the incident.

"One Sunday morning after a very bad night I could not get out of bed. The warder came in and I told him I was ill.

" 'You had better get up', he said; but I couldn't take the good advice.

" 'I can't', I replied, 'You must do what you like with me.'

"Half an hour later the doctor came and looked in at the door. He never came near me; he simply called out 'Get up; no malingering; you're all right. You'll be punished if you don't get up', and he went away.

"I had to get up. I was very weak; I fell off my bed while dressing and bruised myself; but I got dressed somehow or other, and then I had to go with the rest to chapel, where they sing hymns, dreadful hymns all out of tune in praise of their pitiless God.

"I could hardly stand up; everything kept disappearing and coming back faintly; and suddenly I must have fallen." He put his hand to his head. "I woke up feeling a pain in this ear. I was in the infirmary with a warder by me."

"Aren't you a little deaf still", I asked.

"Yes," replied Oscar, "on this side, where I fell in the chapel. I fell on my ear you know, and I must have burst the drum of it, or injured it in some way, for all through the winter it has ached and it often bleeds a little."

This then is the first mention of giddiness and ear discharge, though it had already been noted by Douglas that he was deaf in one ear. It is probable that he had an old otitis media and that the episode just described was a flare-up of this chronic otitis media which caused some labyrinthine irritation and which continued to discharge until some five years later it eroded through the roof of the middle ear to spread to the meninges and possibly adjacent temporal lobe.

R. H. Sherard who visited him in prison at Reading found him to be distinctly hard of hearing. Apart from this episode, prison life seemed to have suited him physically. After he had served a year of his sentence, some friends hearing that he was in the prison hospital made representations to the Home Secretary that he should be released before the end of his sentence on the grounds that his health was being jeopardized by prison conditions.

Two members of the Prison Commission went to Reading to investigate the matter and they were taken to the prison hospital where, unobserved, they saw Oscar entertaining the rest of the inmates of the ward. Polished, urbane, and as talkative as ever, he kept the rest of the ward in fits of laughter, and they hung on his every word. Consequently the visitors had to report back to the Prison Commission that Oscar was certainly not suffering physically and not obviously mentally from his sojourn in prison. After he had served his full two years he came out much fitter than when he went in. He left at once for Dieppe in May 1897, and never returned to England again, spending the remaining three years of his life first at Dieppe, later in Italy, Switzerland, the Riviera and finally Paris. He soon returned to his old habits of over-eating and over-drinking whenever he could afford it and also, alas, to his sexual inversion.

Radio Times Hulton Picture Library.

FIG. 1.—Oscar Wilde shortly after his release from prison.

Artistically he was finished. During the last few months of his prison sentence he wrote "De Profundis", a letter to Lord Alfred Douglas which, even allowing for natural bitterness and histrionic despair, must be one of the most dreadful letters ever written to anyone. After

his release he worked hard for some months on "The Ballad of Reading Gaol", a moving and possibly over-dramatic poem of the execution of a soldier for the murder of his unfaithful wife, and, moving though this ballad undoubtedly is, one can sense throughout it all a whiff of midnight oil. This is quite unlike his previous work, and it is indeed sad to think of the dreadful and deadening effect of prison surroundings on one who had been the very prince of laughter and lightness.

Frank Harris in 1899 notes that Oscar was getting deafer and deafer in one ear, so that they had to change places in the theatre in order to talk to one another. As so often happens, neither Harris nor anyone else mentions which ear was affected, though for reasons which will emerge later it may have been the left ear.

Now, it has been fashionable to decry Frank Harris and to regard everything he said as suspect. But his "Life of Oscar Wilde" which was first published in 1916 was, in the 1938 edition, given a long preface by Bernard Shaw, who was prepared to corroborate much of what Frank Harris said; though he made no bones about Frank Harris' habit of inventing little incidents.

Frank Harris, like Wilde's other biographer Robert Sherard, was always ready to champion any cause or person in which he thought cruelty or injustice played a part. Neither was versed in the art of beating about the bush, or to use a legal term, wrapping it up.

Again Bernard Shaw in his preface to Frank Harris' "Life of Oscar Wilde", referring both to Harris and Sherard, remarks "As to his (Harris) being a hypocrite, his deficiency in this most necessary and invaluable art of social intercourse was equalled only by Mr. Sherard's. Their inability to dissemble their likes and dislikes takes them to the very verge of indecent exposure".

In the main, however, Harris exhibited a strong vein of practical common sense, not unusual in adventurers. He predicted that if Oscar Wilde persisted in his action for criminal libel against the Marquess of Queensberry, the action would fail and then he would be open to prosecution on a criminal charge, which is just what happened.

In 1899 and again during the early summer of 1900 while in Rome, Wilde developed a rash which he attributed to mussel poisoning. He attended several public audiences with the Pope, and attributed his temporary relief from the rash to these audiences. To an artist friend who suggested painting a picture to commemorate the occasion he remarked: "The trouble is that mussels do not lend themselves easily to any art form—of course you could paint their shells, but then you see I didn't eat the shells." This rash has been regarded as a manifestation of syphilis, but it is much more likely to have been an allergy or a dermatitis secondary to vitamin deficiency as the result of his drinking. However, this rash returned after he left Rome and persisted on and off till his death some months later.

Again Frank Harris recounts a conversation he had with Oscar Wilde about this rash.

> "I ate some mussels and oysters in Italy, and they must have poisoned me; for I came out in great red blotches all over my arms and chest and back.
>
> "I'm all right, Frank, but the rash continually comes back, a ghostly visitant. It generally returns after a good dinner, a sort of aftermath of champagne."

On his return to Paris in the later summer of 1900 he continued to drink heavily. Despite generous friends he was always hard up, having wildly extravagant tastes. Fate had turned him not only into a sponge, but also into a sponger. Jean Dupoirier, the owner of the Hotel d'Alsace who befriended Oscar and who actually supported him in his arms as he died, said that Oscar used to drink a litre of brandy a day in the hotel, quite apart from anything he had outside in the way of absinthe or wine which was often quite a lot. Oscar dined out and visited cafés most days except when, as he put it, "I was kept indoors by a sharp attack of penury".

In August 1900 when dining with Douglas in Paris he gave the first hint that all was not well with him, saying: "Somehow I don't think that I shall live to see the new century. If another century began and I was still alive, it would really be more than the English could stand." Douglas never saw him again after this meeting.

He was at this time, thanks to the kindness of the proprietor, living on credit at the Hotel d'Alsace in the Rue des Beaux Arts, a modest but quite respectable hotel in a small street on and parallel with the Left Bank of the Seine off the Rue Bonaparte.

I have visited the hotel and been shown the rooms in which he lived and died. A small back bedroom leads into a sitting room which overlooks a small paved courtyard with two shady trees in it. The daughter of M. Dupoirier was still there though she was but a young girl at the time of Oscar Wilde's death.

In early October 1900 he was troubled with severe headaches and was under the care of the British Embassy doctor and also a French

physician. On October 10, a week before his 46th birthday, a surgeon was called in and Wilde had an operation on the ear; which ear is not known. All we know about this operation is that it was carried out in the hotel, and that afterwards the ear had to be dressed daily for many weeks. It could have been a paracentesis of the eardrum or the removal of a polypus; but the prolonged daily dressing suggests that there may have been an open wound. It would indeed be ironic if he had been submitted to the then fashionable Wilde's incision for mastoid infection; a procedure introduced by and called after his father.

On October 29 he got up and with Robbie Ross went by cab from café to café drinking absinthe. Reginald Turner who tried to moderate Oscar's drinking was told: "You are qualifying for a doctor. When you can refuse bread to the hungry and drink to the thirsty, you may apply for your Diploma."

Of another friend who came to see him, Wilde said: "I showed him what hospitality I could, I even shared all my medicines with him."

On November 28, two days before his death, his great friend Robbie Ross returned to Paris in response to an urgent telegram. He found Oscar in a desperate state, but even so out came a last witticism. Referring to the dark red wallpaper with roses on it he murmured: "This wallpaper is killing me. One of us has got to go." There is no record of his saying anything more. Ross sent for a priest, Father Dunne of the English Passionists, in order that Oscar might be received into the Catholic faith. Though just conscious Wilde could not speak, but signified his assent to the priest's questions with a movement of one hand. Which hand, I wonder? Ironic that one who was a very prince of the spoken word was robbed of this faculty before unconsciousness overtook him. A study of his handwriting suggests that he was right-handed and this aphasia could well have been due to an abscess in the left temporal lobe secondary to otitis media. Of course, his aphasia may have been part of the clouding of the senses which so often precedes the final coma of intracerebral suppuration. If he had suffered from uncomplicated leptomeningitis then delirium sufficiently wild to have been noteworthy would have preceded the final coma. Thus it seems likely that he had a temporal lobe abscess in the dominant hemisphere secondary to chronic suppurative otitis media.

At any rate the priest received Wilde into the Roman Catholic Church and administered Baptism and Extreme Unction. Soon after he lapsed into coma to die some thirty-six hours later.

If my assumption as to the cause of his death is correct, then his habits and way of life played little or no part in his early demise. The skin rash attributed to mussel poisoning could well have been allergy or a vitamin deficiency such as is often associated with chronic alcoholism.

However, whether or no he by his acts encouraged his own demise, there can be no doubt that by his egotism and by his self-indulgence he brought about his social and artistic suicide. He once said:

> "To fall in love with oneself is the beginning of a lifelong romance."

In the only work that he wrote after coming out of prison, "The Ballad of Reading Gaol", there occurs repeatedly the theme:

> "For each man kills the thing he loves,
> Yet each man does not die."

I think that Oscar Wilde must have been thinking of himself when he wrote this.

The one infirmity which is mentioned from time to time by his contemporaries was deafness in one ear. His final illness was ushered in by an operation on one ear, and I cannot do better than quote Frank Harris who said:

> "The sore place in his ear caused by the fall when he fainted that Sunday morning in Wandsworth Prison Chapel formed into an abscess and was the final cause of his death."

Frank Harris was right when he predicted the result of Oscar Wilde's libel suit against Queensberry and on the evidence available then, and with our knowledge now, I think that his is the likeliest explanation of the last illness and death of Oscar Wilde; and I offer it to you as it stands because after all Frank Harris had the advantage over all of us and over many who have written about Wilde since, that he knew the patient well.

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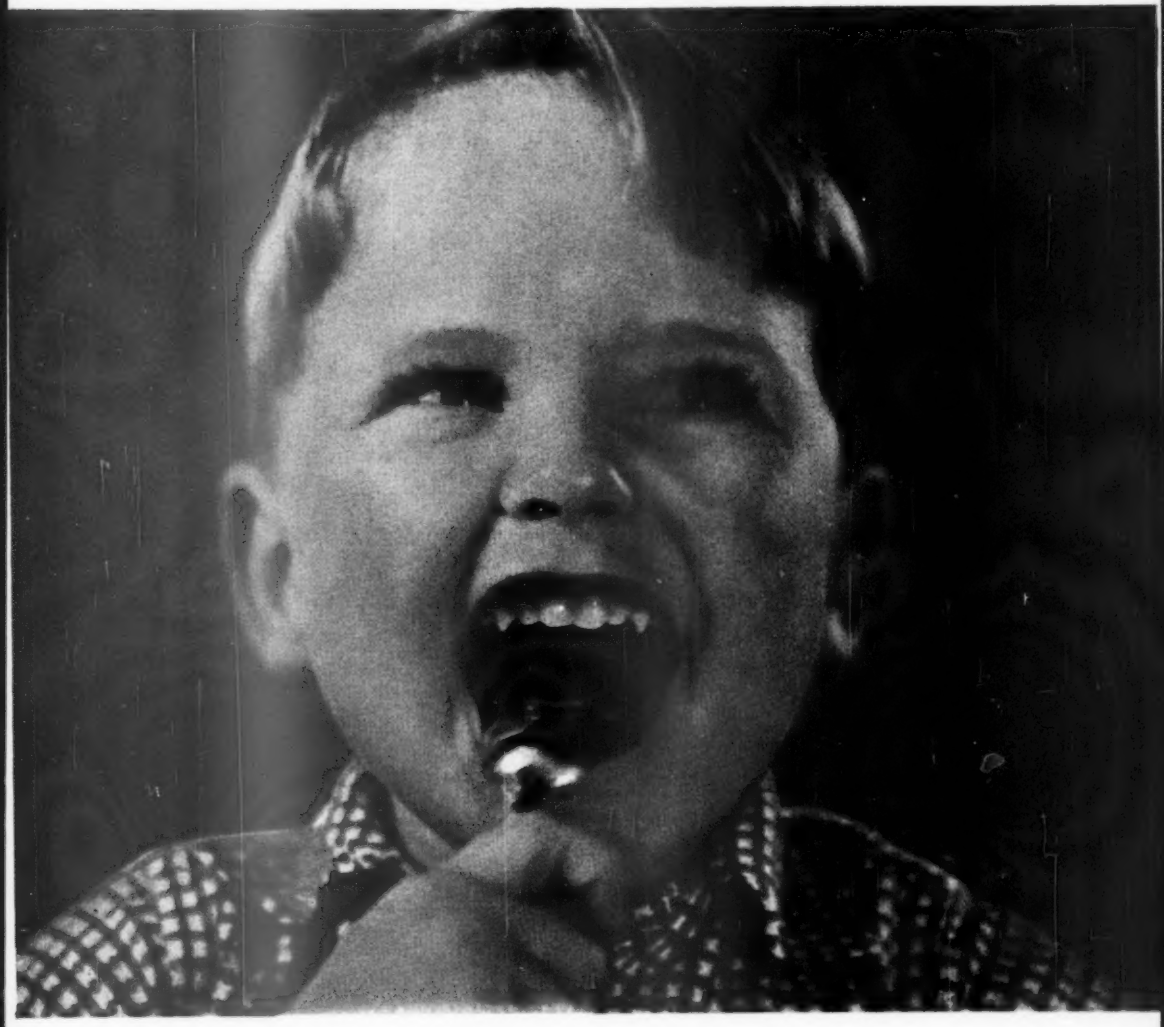

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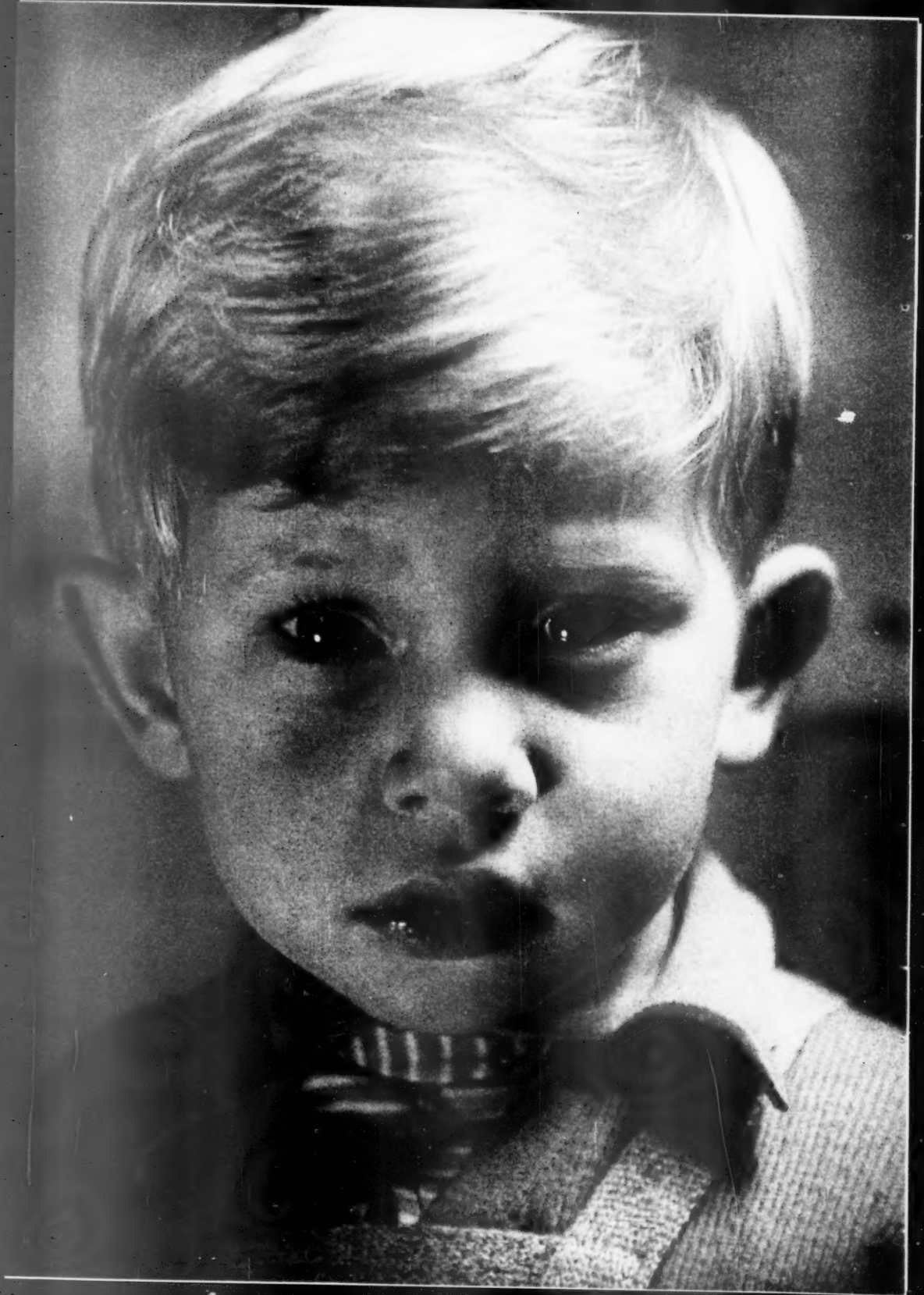

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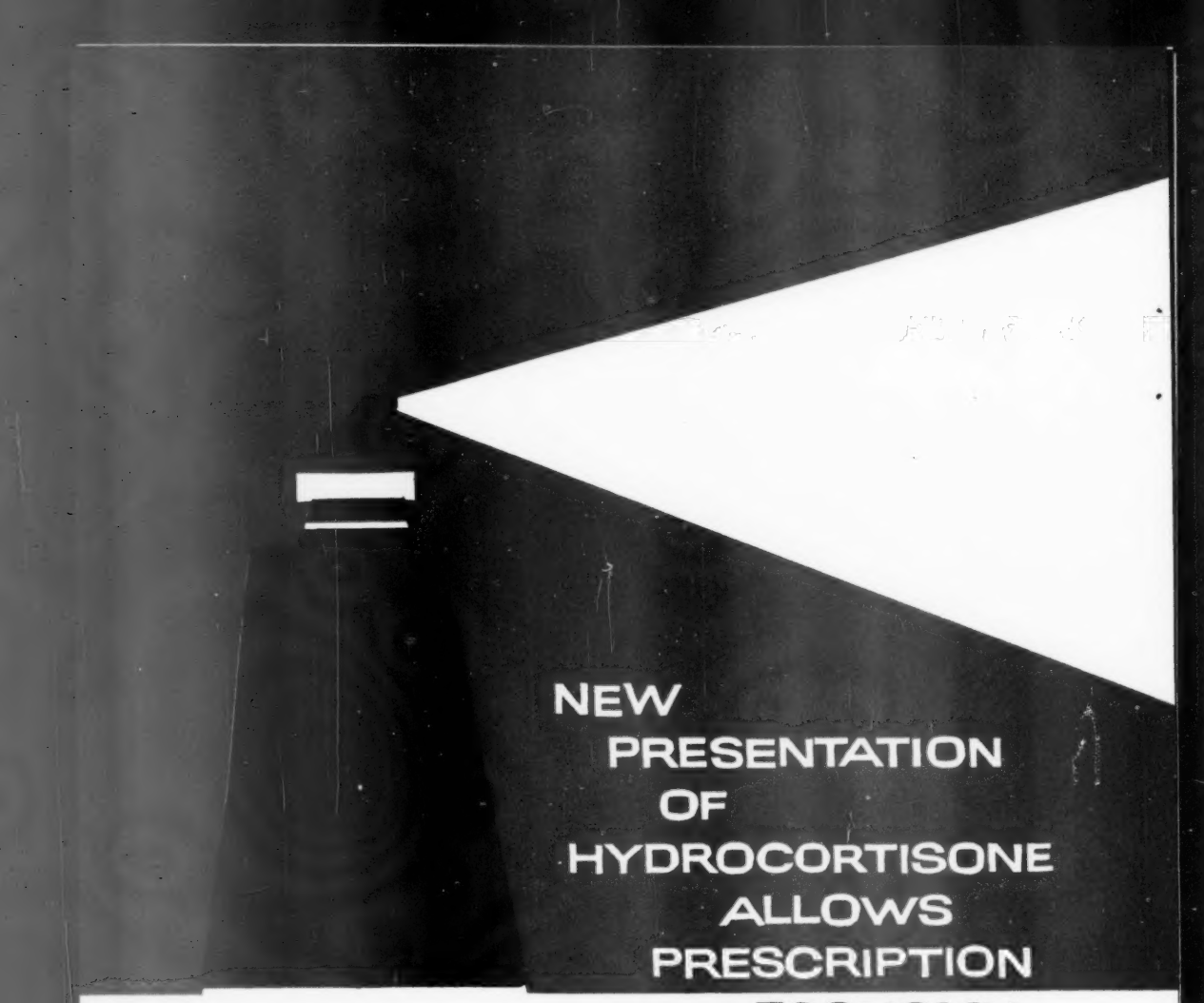

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Section of Physical Medicine with Section of Orthopædics

Chairman—KENNETH LLOYD, M.R.C.P.
(President of the Section of Physical Medicine)

Meeting
October 7, 1958

DISCUSSION ON THE MANAGEMENT OF THE DEFORMITIES OF THE RHEUMATOID HAND [*Abridged*]

Dr. D. A. Brewerton (London):

Joint Deformities and Their Prevention

The problem with this subject is that there are too many variables. No two patients are really alike; and, even if they were, they would be subject to uncontrollable fluctuations in joint inflammation. It is difficult to avoid talking in terms of clinical impressions, and several types of treatment, each applied to a small group of patients. Therefore, I have preferred the other approach of studying the deformities themselves, to see which ones are common and important, and why they occur, in the hope that it will simplify treatment and place it on a more rational basis.

Ulnar deviation.—There are, in fact, four important anatomical changes: ulnar deviation of the fingers; medial subluxation of the proximal phalanges into the grooves between the metacarpal heads; and their anterior subluxation, so that it is really an antero-medial subluxation or dislocation; and dislocation of the extensor tendons into the grooves between the metacarpal heads.

The effect on function may be slight, even when the deformity looks severe. The commonest disability is loss of active extension of the fingers due to the inefficient pull of the dislocated extensor tendons. This makes it difficult to grasp a large object unless the object can provide resistance against which the fingers can be extended passively. Occasionally the medial instability of the fingers weakens the grip between finger and thumb, but this is a relatively minor problem. The point that matters is whether the ability to flex the fingers is maintained, and, in fact, it is maintained as often as in patients without ulnar deviation.

The causes of ulnar deviation are complex, and still not completely clear. Most important are the destructive changes in and around the metacarpophalangeal joints. Then, there is a lateral strain every time the patient opens a door, lifts a saucepan or wrings out a dishcloth. Intrinsic muscle contractures add their contribution and simple muscle contraction can aggravate the anterior subluxation. Finally, once the extensor tendons are dislocated, their pull is no longer along the line of the fingers, and they accelerate the process.

Prevention is only possible before the stage of subluxation. Early deviation associated with inflamed, swollen joints may recover with rest and general measures; but after that stage the results of treatment are not convincing. Once antero-medial subluxation begins it seems to go on to major deformity, and no conservative measure will stop it. Night splints can have no effect once the deformity is established, particularly when the hand is exposed to constant strain throughout the day doing household tasks.

Lateral instability of the thumb.—Instability at the metacarpophalangeal joint is actually commoner than ulnar deviation of the fingers, and more likely to interfere with function. Treatment can only be surgical, but in the small proportion of patients suitable for arthrodesis function is usually improved.

Instability of the interphalangeal joint of the thumb is comparatively rare, but it may be so severe as to make the thumbs virtually useless. Again, arthrodesis may produce excellent results.

Inability to flex the fingers is the most important deformity in the rheumatoid hand; it is common, and a loss of range of even a few degrees may have a profound effect on function. The essential movements are flexion of the metacarpophalangeal and proximal interphalangeal joints of the ring and little fingers, because these fingers often have to grip a long handle against the palm of the hand. By contrast, the index and middle fingers usually work with the thumb, and for this their joints have to flex through only half their normal range. In rheumatoid arthritis it is unusual for stiffness of these two fingers to be so severe that it interferes with the handling of small objects.

There can be no doubt that this loss of finger flexion is mainly due to the inflammatory processes in and immediately round the joints, but there are other factors, particularly flexor tendon lesions and contractures of the small muscles of the hand.

Rheumatoid involvement of the flexor tendons may prevent active flexion of a finger, even when there is a full range of passive movement. This condition is not as common as a rheumatoid trigger finger, but in many ways it is more interesting. The trigger finger often cures itself or can respond to a hydrocortisone injection, but this is aggravatingly persistent and may lead to secondary joint stiffness in an awkward position.

Intrinsic muscle contractures are responsible for a high proportion of the hyperextension deformities of the proximal interphalangeal joints, and these may interfere seriously with finger flexion. At first the passive range of flexion is normal but the initiation of active flexion is hesitant and sometimes painful due to the awkward starting position. Later the passive movement may be lost and all the fingers may become fixed in a hyperextended position. There are two points to be made from the viewpoint of prevention. This type of contracture starts with "spasm". In the early days it can be overcome with gentle manipulation; it can disappear within a few days of starting cortisone therapy; and reappear when it is stopped. Also, three years may elapse between the onset of this "spasm" and the first signs of hyperextension. During this period prevention ought to be possible. The patients are trained in the habit of extending their metacarpophalangeal joints repeatedly while keeping their interphalangeal joints flexed . . . and the physiotherapists do this as a routine in their treatments.

Loss of extension.—While mild loss of extension is common, it is surprisingly rare for it to be bad enough to interfere seriously with function. This difference between flexion and extension has important implications in treatment.

Stiffness of the thumb is common and important. In 30% of patients loss of internal rotation is severe enough to interfere with opposition—and in 10% it is coupled with restricted abduction, a combination that makes the handling of small objects between finger and thumb very clumsy indeed. Less commonly, thumb abduction is so limited that the handle of a walking stick or crutch cannot be forced between finger and thumb.

Of all the movements in the hand those most important to retain intact are flexion of the ring and little fingers, and internal rotation, adduction and abduction of the thumb.

Some Basic Principles in Treatment

Prevention is only really effective in the early stages, when the joints are inflamed and before lasting deformities have begun. At this stage treatment should be based on the deformities that are likely to occur and become important to the patient. To wait and tackle the deformities as they begin is to miss the best opportunity.

Rest is difficult to prescribe, but it is undoubtedly the most important measure available. Other treatments are of little use if the patients constantly drive themselves against pain and fatigue to all sorts of activities that are harmful to their hands. Many of them dread becoming crippled and unable to look after themselves or their families; until they are helped to come to terms with their disease, they may refuse help in an attempt to prove to themselves that they are normal. Other patients can be helped considerably by instruction from occupational therapists or physiotherapists who have studied the techniques of working while placing a minimum of strain on painful joints.

Splints.—Hand splints may be used either to rest the hand and diminish inflammation or to correct deformity. Undoubtedly the best way to mobilize an acutely painful hand is to *immobilize* it on a splint. Unfortunately two errors are almost universal among non-medical staff. One is a confusion of purpose, attempting to combine rest with correction of loss of extension of the fingers. This puts a strain on the painful joints, and neither aim is achieved. The other error is to make a relatively flat splint, so that the thumb is held in external rotation. Splints for rheumatoid patients should be designed to maintain opposition as much as possible.

Physiotherapy.—Patients who have recently acquired rheumatoid arthritis need sympathetic understanding, general advice and a feeling that something is being done. These a good physiotherapist can provide, and it is quite right that she should. In fact, this is probably the main reason for our seemingly endless prescriptions of "wax and exercises". *Heat* undoubtedly relieves pain temporarily but there is little to choose between one form of heat and another. Wax is particularly comforting, and convenient as a preparation for exercises, but it certainly does not deserve to be treated almost as if it were specific for rheumatoid arthritis; hot water is probably as good. *Exercises* have their greatest value when voluntary movement is prevented by severe pain, a tendon lesion or a muscle contracture. Physiotherapists should be taught to concentrate more on the joint movements whose loss most often leads to disability—and

that prevention of intrinsic muscle contractures should become a routine in their treatment.

Mr. Ronald Furlong (London):

The management of deformities of the rheumatoid hand consists, essentially, in treating the patient with rheumatoid arthritis with additional treatment to the hand. The earliest signs of rheumatism may not be easy to recognize, and in fact they are often undiagnosed for a long time. A rather diffuse ganglion on the dorsum of the hand may be the first indication of a coming generalized affection. Tenosynovitis fungosa, that is to say a granuloma, non-infective in type, of synovial tendon sheaths, is now recognized to be a manifestation of rheumatoid arthritis. Difficulty arises, however, at this point with histology. Frequently the histological picture of this condition reveals a granuloma so similar to tuberculosis as often to be confused with it. Caseation is never present but the arrangement of the cells and the method of advancement of the granuloma is highly reminiscent of tuberculosis of subsynovial tissue. Clinically there is, of course, a strong similarity between tuberculosis and rheumatoid arthritis in the way they invade and behave in relation to synovial tissue. Extirpation of a rheumatic ganglion on the dorsum of the hand does not prevent later involvement of other joints any more than excision of a local focus of tuberculosis will prevent spread elsewhere.

The wrists may also be involved, and there is no better way of getting rid of pain in such an instance than by applying a splint. Therefore, if the patient is in distress on account of painful, swollen, and tender wrists these should be immobilized, but it must be realized that this immobilization, though making the patient comfortable, may stiffen the wrists permanently. Stiff wrists, however, in context with this condition, are of no disadvantage.

In the matter of fingers the situation is entirely different. Immobilization of the fingers can be disastrous. Occasionally, a patient may have to wear a splint at night in order to get any sleep at all, but the risks of avoidable stiffness must be recognized. If, however, the splint is removed for as long as possible during the day, and the patient is encouraged to mobilize the hand, this disadvantage may well be offset.

Deformity may be the result of two factors: firstly the posture of the fingers or hand, and secondly the appearance or contour of the joint. The contour of the joint is the result of the rheumatoid infiltration and little can be done to improve this. The deformity which is due to posture is a different matter, and discussion has arisen as to its origin. One of the obvious effects of the granuloma of rheumatoid arthritis is to soften the structure in which it is developing. This structure may be ligament or tendon, and in either case it is involved by being in close contact with synovial membrane, the tissue first involved in rheumatoid arthritis. Therefore, if ligaments or tendons become softened and weakened. they are liable to be stretched or ruptured during the course of normal existence.

Common deformities include the dropped finger due to erosion and rupture of the extensor communis digitorum tendon, dropped thumb due to erosion of extensor longus pollicis tendon, and hyperextension of the proximal interphalangeal joints due to rupture of the flexor sublimis digitorum tendon; all these are due to erosion of capsule of tendon permitting gravity and normal use to produce the deformity. Ruptured tendons may be sutured with good results.

The patient may be much disabled by stiffness of joints which is the end-product of this disease. Stiffness is aggravated by stillness, and is reduced by movement. The doctor, therefore, is presented with a dilemma; should he encourage stillness to protect tendon and ligaments from damage, or should he encourage movement to prevent or reduce stiffness? The patient usually takes the initiative because of the realization that salvation lies in continued movement. Lively splints have been devised which permit some movements while protecting the joint structures from others which may be harmful. Normally, these splints are too cumbersome to be of any real value to the patients, who generally only wear them when they visit the doctor. When faced with the dilemma of the stiff hand the doctor should encourage movement by all available means to provoke mobility and prevent stiffness. To run the risk of reducing function by tendon rupture at least secures mobile fingers which are more likely to be useful than stiff ones.

Surprisingly enough patients do not usually make great complaint about the deformity of their hands. It is as though the deformity of the hand is in context with their other limited powers, and they do not find it an outstanding or remarkable trouble. It is possible that the salvation, no doubt to be obtained by patients of later generations, will be derived more by improvement in general therapy than by devices or ruses thought up by the doctor. Limited finger function does not disturb the patient as much as the doctor thinks it should. Therefore, let the patient beware against over-enthusiastic doctors.

Mr. O. J. Vaughan-Jackson (London):

Attrition Ruptures of Tendons as a Factor in the Production of Deformities in the Rheumatoid Hand

Rheumatoid arthritis is a progressive disease and that its deformities are also progressive is only too manifest. They are familiar and extensive, producing high degrees of disability. That they are for the most part also very gradual leads in more ways than one to their receiving far less attention than they deserve. Patients become slowly aware of them, and slowly crippled. There is seldom anything very particular to complain of about any one joint—rather is there a general complaint of many joints—and, since the condition is labelled rheumatoid "arthritis" (it is of course very much more than this), its mechanical disabilities tend always to be interpreted as products of damaged *joints*, often to be shelved as nearly hopeless as individual problems and only to be tackled on general lines. Surgery has played a small part, for the most part confined to arthrodeses or arthroplasties in the lower limb, when all else has failed. Since rheumatoid patients seem, as a class, well supplied with fortitude and manage to achieve astonishing functional adaptations in their damaged hands it is not surprising that the rheumatoid hand has not received very much analytical attention in the past. That such *established* functional adaptations are a contra-indication to surgical meddling does not conflict with another truism, namely that surgical interest during the early stages can often, through timely intervention, reduce the degree of adaptation that will be necessary. For in rheumatoid arthritis one deformity leads to another, and early attention is essential.

The truth of all this was brought home to me in 1946 and 1947 by the discovery of 2 cases of painless spontaneous rupture of the common extensor tendons on the dorsum of the wrist caused by attrition on a lower end of ulna roughened by arthritis. In each case a rough spicule of bone on the lower end of the ulna had worn a hole in the floor of the dorsal tendon compartment through which it had attacked and severed extensor communis to the little finger. The extensor to the ring finger had then in its turn been severed and each patient, having noticed with interest the abrupt painless spontaneous dropping of the little finger at the metacarpophalangeal joint without being moved to seek advice, came hurriedly up for assistance when the ring finger followed suit equally abruptly a week or two later. We explored both wrists and, in the first, the finding at operation of the extensor to the middle finger abraded half-way through, as well as complete severance of the extensors to ring and little fingers, made the mechanism quite clear. The abrasion was present over approximately one inch of the ulnar margin of the tendon and was quite clearly due to a combination of abrasion across the margin of the tendon in pronation and supination, and along its length as the tendon moved to and fro in flexion and extension movements. The ends of the severed tendon were not at first easily discernible as they were connected by thin bluish-white strands but they were easily dissected free. This bluish-white strand is, I am sure, what has crept into the textbooks as a "stretched degenerate tendon" giving rise to the perennial legend of stretched rheumatoid tendons. This strand only begins even faintly to suggest a stretched tendon when the rupture is months old. In the early stages it is *manifestly* the collapsed tube of paratenon within which the tendon has been ruptured.

A search for reports of similar cases in the literature in English produced not one case for thirty-one years back, though ruptures of extensor pollicis longus were numerous. Accordingly the 2 cases were published as curiosities (Vaughan-Jackson, 1948). Since then there has been a striking increase in the number of cases—at first a trickle, now a steady stream—so that I have been operating approximately once a fortnight on one of these cases, and a steady succession of cases is being reported by other surgeons. In every case the pattern of attrition is faithfully reproduced, a roughened ulna severing extensor communis tendons seriatim from the little finger towards the index. In 30 consecutive hands the abrading spicule has been visible, but it has to be looked for. It tends to be hidden under a pouting bulge of thickened synovial membrane or by a valvular arrangement of the layers of soft tissue forming the floor of the tendon compartment. Figs. 1–4 show a typical case.

All these cases have been treated simply by the removal of the lower end of the ulna with its abrasive spicule and the repair of the severed tendons. The repair in the early cases was always by means of free tendon grafts (e.g. of palmaris longus or a toe extensor) but I prefer more and more to transfer an available tendon such as extensor proprius to the index, or switch a strip from an intact extensor across to the distal end of the severed one. The results have been uniformly encouraging—normal extensor power is restored in nearly every case. The failures have been due to poor technique, for example adherence of suture lines. Cobbling several distal tendon stumps together as one "common extensor" does not work; it alters the line of pull of the tendons far too much.

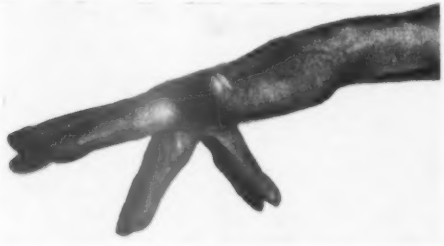

FIG. 1.—Shows the inability to extend ring and little fingers.

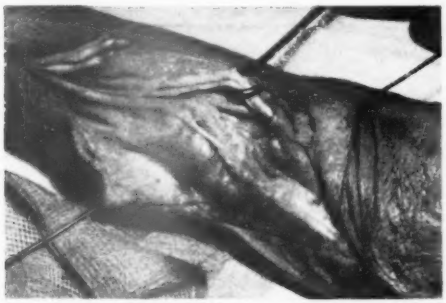

FIG. 2.—Findings at operation. Bulbous tendon ends at the left. Lowest one joined by a long thin strand of paratenon to the corresponding end in the lower right corner of the incision. This strand passes close to the hole over the prominence of the ulna, seen as a black dot in the middle of its length. The partially frayed area on the extensor to the middle finger can be seen held up in the grip of the hook.

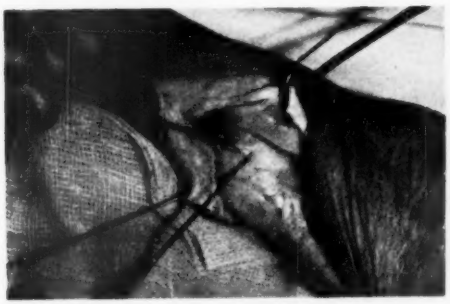

FIG. 3.—Closer view of the hole in the floor of the tendon compartment held open by two fine hooks. The partially abraded tendon is seen in the grip of the button hook retractor.

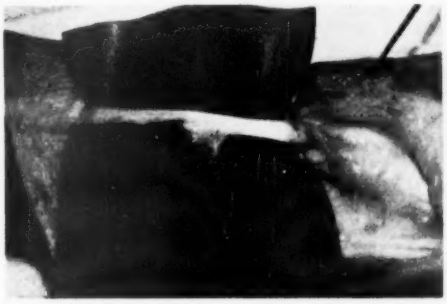

FIG. 4.—To show the area of attrition along the ulnar margin of the extensor tendon to the middle finger.

This is a clear-cut recurring clinical picture of a lesion *that can be repaired.* It is not a picture of rheumatoid degeneration leading to spontaneous rupture—indeed the tendons are remarkable for their macroscopic and microscopic normality considering the rheumatoid battlefield they traverse. But in any case the evidence of pure mechanical attrition is overwhelming.

These things ought to be detected early on, yet manifestly they are very commonly missed though the evidence is all there if we will but interpret it. It is easy enough to understand how someone with severe rheumatoid arthritis may fail, among her many troubles, to notice the painless dropping of a finger but what is baffling is how the other common type of case gets missed—the patient with a mild rheumatoid arthritis of the wrist only who notices at once when a finger drops, and seeks help.

I have now, with the assistance of Dr. W. S. Tegner and Dr. Michael Mason, got a promising selection of attrition ruptures of flexor tendons in the carpal tunnel. Here again there is a quite typical clinical picture—the patient notices nothing until a flexor profundus is severed. The alert surgeon explores the carpal tunnel to find a scene, as it were, of carnage and destruction with every tendon in the tunnel in tatters. In one example of this the cause was not rheumatoid arthritis but a Colles' fracture. In another patient with rheumatoid arthritis the attrition was due to a roughened bare area on the proximal pole of the scaphoid. Here the presenting symptom (apart from the rheumatoid joints) was sudden stiffness of the index in extension—the sublimis had long since parted without the patient's knowledge and it was only the final rupture of his profundus that he noticed.

In another patient, an elderly woman, the lower end of the ulna had attacked the flexors instead of the extensors. But in addition she displayed a different kind of attrition—a longitudinal combing out of a flexor tendon by

its excursion to and fro over a spicule on the proximal row of the carpus. This was a new kind of attrition. Yet soon it was found again in another patient in extensor carpi radialis longus. The tendon was reduced to a transparent sheet with a few fibres only still continuous. In the other wrist the carpal extensors were actually severed. This woman's main troubles were due to the subluxation of the first wrist and the complete dislocation of the second. I suggest that her wrist could not dislocate completely until the wrist extensor tendon was severed. Might not then a timely removal of the abrading agent have saved her wrist from subluxating at all or at any rate put off the evil day?

This woman illustrates only too well how one thing leads to another in these hands. We rescued these wrists by arthrodesing them. But she also had hyperextension deformities of the proximal interphalangeal joints of several fingers in both hands, with the usual accompanying flexion of the terminal joints. The interesting thing is that the simple reduction of the dislocation of her wrists immediately corrected these hyperextension deformities of the proximal interphalangeal joints and restored her fingers to a position of function. That this success will not last long for her, as she has a rampaging malignant rheumatoid arthritis that will not be controlled, does not detract from the lesson it has for us.

This hyperextension deformity of the proximal interphalangeal joint is a very interesting one.

The only way I can explain how a dislocation of the wrist can produce it is that the projection of the dislocated carpus forwards stretches the profundus tendon round it, thus pulling on the terminal phalanx and flexing it, but also tightening the lumbrical and through this tightening the lateral bands of the extensor expansion and extending the proximal interphalangeal joint. Some hold that most of these hyperextension deformities are due to tight intrinsics. In my experience very few actually are. But if a sublimis tendon is borrowed to carry out an opponens transfer, for example, a common minor complication is a hyperextension deformity of the proximal interphalangeal joint. How many then of these deformities in rheumatoids may be due to a sublimis severed in the carpal tunnel by the kind of attrition I have described? It is time we found out.

Again, a mallet finger deformity is often accompanied by hyperextension of the proximal interphalangeal joint—how many of these in rheumatoids are caused by attrition ruptures of the terminal attachment of the extensor apparatus over a roughened head of the middle phalanx? I now have three cases of boutonnière deformities at the proximal interphalangeal joint due to attrition rupture of the central slip of the extensor apparatus over rough bare bone on the articular surface of the head of the proximal phalanx due to rheumatoid arthritis. If such attrition can happen there it can, I am sure, sometimes occur at the terminal joint and cause a mallet finger.

What normally keeps the common extensor tendon on top of the metacarpal head? Kaplan (1953)stresses the importance in this respect of the attachment of this tendon's deep surface to the base of the proximal phalanx. Could severance of this attachment by attrition sometimes set the tendon free to fall into the adjacent valley between the metacarpal heads? If so it might be the precipitating factor in that otherwise inexplicable ulnar deviation that we see so often.

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Proceedings of the Royal Society of Medicine

Vol. 52
135

Section of Comparative Medicine

President—F. O. MacCallum, M.D.

Meeting
October 8, 1958

Some Aspects of Immunity in Virus Diseases [*Abstract*]

PRESIDENT'S ADDRESS

By F. O. MacCallum, M.D.
London

Virology is one of those subjects, formerly the prerogative of the biologist, in which a great increase in knowledge has been obtained in recent years by the introduction of new techniques by workers in other disciplines such as biochemistry and biophysics. Some of these recent advances have been discussed in this Section from time to time, but the subject of immunity in virus diseases of man has not been discussed in this Section since Professor S. P. (now Sir Samuel) Bedson's Presidential Address in 1937 on "Some Reflections on Virus Immunity" and a brief discussion on "Immunity to Viruses" by Ledingham, Doyle, Andrewes and McClean in 1943. It therefore seemed a suitable time to consider this subject again, including some results of current studies.

At times the suggestion has been made that the mechanism of immunity in virus diseases is quite a different process from that occurring in bacterial diseases; at other times new facts brought to light suggested to others that the mechanisms are inherently the same.

Bedson in 1937 rightly stressed the point that one should not generalize for, just as there are considerable differences between bacteria such as pneumococci, tubercle bacilli and cholera vibrios, one can expect differences between viruses. He then discussed the three commonest theories of the basis of virus immunity which had been put forward in the previous fifteen to twenty years, and finally stated his own views. The current theories at that time were:

(1) Active immunity to a virus could not be engendered apart from actual infection.

(2) Immunity to a virus was in part, or in whole, a tissue immunity.

(3) Protective antibody had nothing really to do with the virus but was produced in response to an antigen elaborated by the tissues of the host, and performed its protective role by uniting with the susceptible cells.

These items continue to be a centre of argument but it is now generally agreed that antibody combines with virus to neutralize it. Bedson and a number of other workers who have discussed this subject more recently have also suggested three mechanisms which are described in somewhat different terms.

These three types of virus immunity are:

(1) Persistence of virus without neutralizing antibody for virus.

(2) Persistence of antibody without virus.

(3) Persistence of virus and persistence of antibody.

Humoral immunity has received the strongest support as being the predominant mechanism in most virus infections. Antibodies are something relatively tangible which one can measure by various tests *in vitro* and *in vivo* but the presence of tissue immunity by itself is much more difficult to assess.

The introduction of the use of the fertile hen's egg and, more particularly, since 1949 the use of tissue cultures has resulted in even more intensive investigation of the mechanism of the inactivation of virus by neutralizing antibody in the blood. However, in spite of the many advantages which the technique of tissue culture has in comparison with experiments in animal hosts, the cultures are not an exact model of the natural conditions, and the condition of primary hypo- or agammaglobulinæmia in man which offers suitable subjects for investigating this problem, has been recognized at an opportune time (Bruton, 1952; Jean, 1953; Good, 1954). The term agammaglobulinæmia has priority over hypogammaglobulinæmia where they are considered synonymous but, as nearly all these patients have some

gamma globulin circulating, the term hypogammaglobulinæmia will be used here. No reference to a similar condition in animals has been found. Most of my Address will be concerned with remarks on this subject, and will conclude with a few remarks on immunological reactions following infection with vaccinia virus.

The first report of a case of primary hypogammaglobulinæmia in a child was that of an 8-year-old boy by Bruton in the United States of America in 1952. Since then a small number of child patients of both sexes have been found, with barely detectable levels of gamma globulin and otherwise normal serum proteins, who are subject to recurring bacterial infections. The disease appears to be congenital and is possibly due to persistence of the early fœtal state, for some reason as yet undetermined. All the cases in children in the United States have been males, including brothers and uncle-nephew relationships, and Janeway, *et al* (1953) would like to class it as a sex-linked mendelian recessive characteristic. However, in addition to cases in young males, the condition has also been reported in female children in France (Delaitre and Fonty, 1955) and England (Pearce and Perinpanayagam, 1957) and a number of other such cases are at present being studied in Great Britain. Studies are also now in progress to determine whether any fundamental difference exists between the cases of male and female children.

In addition cases in adults have also been found (Young and Wolfson, 1954). The adult cases may be idiopathic or associated with disease of the reticulo-endothelial system.

An excellent review of the subject was made by Good and Varco in 1955, and no discussion of the general subject will be given here. We are only concerned with two of the main characteristics, which are a failure to produce antibody after infection with viruses, or after injection of virus vaccines. However, in contrast to the serious results reported when bacterial infections occur, virus infections do not appear to be any more frequent or severe than in normal people with apparently normal antibody production. This is seen most strikingly in the case of smallpox vaccination which appears to run a normal course although, as will be mentioned subsequently, vaccinia infection can result in serious disease.

After several cases of hypogammaglobulinæmia had been reported in this country (Grant and Wallace, 1954; Hutchinson, 1955) a Medical Research Council Committee was formed in 1955 to help to co-ordinate the study and treatment of cases found in Great Britain. Serum collected at different times from most of these patients has been examined for the presence of various bacterial and virus antibodies at the Central Public Health Laboratory, Colindale. Only a few results of interest will be quoted here in general terms, as the work is incomplete and will be published later as part of a full report. [A number of tables were shown, demonstrating particularly the antibody levels to the three types of poliomyelitis virus before and during treatment.]

The group studied includes male and female children and adults. The size of the groups is too small to permit generalization, but the following points may be made:

(1) All those who have been vaccinated against smallpox prior to being diagnosed as hypogammaglobulinæmia cases have had a normal reaction with normal healing.

(2) All but one of the young males has been antibody-free before commencing treatment. One boy had low titre antibody to one type of poliomyelitis virus. All the young females have been devoid of antibody.

One young female described by Pearce and Perinpanayagam developed paralytic poliomyelitis from a type 1 virus infection, but has made a fairly good recovery. She had received 14 weekly doses of 750 mg. gamma globulin at the time of onset of her illness and this dose was continued throughout her illness. Her neutralizing titre at the presumed time of infection was probably 1/8–1/16 against 100 TCD_{50} in monkey kidney cultures in roller tubes. (This titre can only be approximate as no serum was collected at the onset of her illness, nor until some weeks later when she was on the same dose of gamma globulin.)

(3) Children in families where the parents and siblings have antibodies to herpes simplex have had few, if any, obvious attacks of clinical herpes simplex. This is also true of adults. One adult female with hypogammaglobulinæmia had poliomyelitis and herpes simplex neutralizing antibody.

(4) In general, those injected with influenza or poliomyelitis vaccine have failed to produce antibody. One adult female who made a spontaneous recovery developed antibodies during the course of an attack of influenza A Asian type, and about eight months later had a good antibody response to one dose of influenza vaccine, and also responded to two doses of poliomyelitis virus vaccine.

(5) The antibody titres to the three types of poliomyelitis virus in the patients' sera were not regularly directly proportional to the titre of these antibodies in the gamma globulin used for weekly injections. For example, if the gamma globulin titres for types 1 and 2 were 1/500 in each, the patient's titre might be 1/4 for type 1 and 1/64 for type 2.

These various points are now being investigated in more detail. It is possible that several different patterns will be found in different sexes and ages.

Vaccinia

Other information bearing on the general subject of the immunological response in virus infections is available from the results of investigations of cases of vaccinia and their treatment with gamma globulin, particularly by Kempe *et al.* (1956) and also from the results of studies of the ordinary vaccination reaction when vaccination is carried out up to two days after injection of vaccinia-immune gamma globulin, by Gispen *et al.* (1956).

Summary of the Possible Types of Immune Response to Vaccinia Virus

(1) Normal "take" and normal level of gamma globulin in serum with development of neutralizing antibody.

(2) Normal "take" but hypogammaglobulinæmia present and no detectable neutralizing antibody develops.

(3) Normal "take" in the presence of passively administered antibody.

(4) Abnormal "take" followed by:

(*a*) Generalized vaccinia with normal skin with slow development of antibody and recovery.

(*b*) Generalized vaccinia with eczema. May have normal gamma globulin, development of antibody, recovery or death. May have normal gamma globulin but no neutralizing antibody development, and when given gamma globulin may recover or die.

(*c*) Serum from one fatal case of vaccinia gangrenosa was said not to contain gamma globulin but neutralized virus on choriocallantoic membrane of developing chick embryo.

Summary

It has been customary to suggest that protection against infection, or at least protection against disease after infection with poliomyelitis and pox viruses and possibly herpes simplex, is largely due to the development and action of neutralizing antibody which is found in the gamma globulin fraction of serum. It is possible that minute amounts of antibody which cannot be detected by the relatively crude tests now available, but normally adequate for protection, are present in some of the types of cases listed above.

However, the information available on a comparatively small number of patients in U.S.A. and Great Britain indicates that there are individuals in whom deficiencies of gamma globulin and virus-neutralizing antibody may be relatively unimportant, and further thought should be given to the problem of other defence mechanisms that may be brought into play.

Acknowledgment.—I wish to acknowledge with thanks the help of the many doctors who supplied sera from the patients, and Dr. A. D. Macrae and Mrs. J. McCapra for carrying out the poliomyelitis antibody neutralization tests, which were the main topic of discussion in the lecture.

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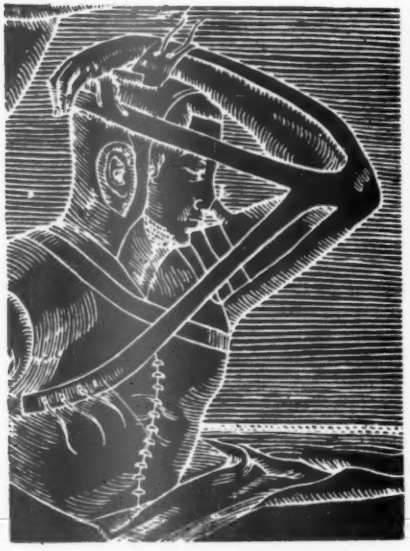

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Clinical Section

President—Sir ERIC RICHES, M.C., M.S., F.R.C.S.

Meeting
November 14, 1958

Chyluria Due to Filariasis. — B. GOTTLIEB, M.R.C.P.

S. C., male, aged 27. Pakistani.

History.—Arrived from Pakistan in September 1958. One sister, father and a cousin have all been treated for "filariasis". Recurrent attacks of "malaria" since boyhood; last bout two years ago. Nine years ago: infection of left forearm which subsided following operation. The epitrochlear gland was enlarged at that time.

Seven years ago and again on 2 occasions five years ago: persistent fever with urticaria. These infections were considered to be due to typhoid and were different from "malaria" in that the fever did not fluctuate and was persistent. Several attacks of fever since then, most of which were regarded as due to "malaria". Most recent attack three months ago was associated with sore throat.

22.8.58: Chyluria whilst in Italy *en route* for England. Felt well during that time, but two or three nights previously may have had a slight fever. Recent weight loss of 6 lb.

On examination.—He was thin. Small left epitrochlear gland palpable, no other obvious lesion detected. Urine milky white. 2.10.58 to 21.10.58: In-patient at St. Mary Abbots Hospital: afebrile; pulse 72–88. Chyluria persisted; particularly marked in morning specimens.

Investigations.—Urine: Protein 0·9 to 2·4 grams%. Leucocytes, mainly lymphocytes, with a few polymorphs and some R.B.C.s. No microfilaria seen. Total lipids 408 mg./100 ml., cholesterol 68 mg./100 ml. Examination by dark ground illumination showed numerous tiny refractile particles presumably of lipid nature.

Blood: Two consecutive night specimens showed active mobile organisms resembling microfilariæ, which was confirmed subsequently on staining. Serum cholesterol 260 mg.%, lipids 1·02 grams/100 ml.

Proteins: Total 7·0, albumin 4·9, globulin 2·1 grams/100 ml.

Blood count: Hæmoglobin 16·1 grams%, W.B.C. 8,300 (polys. 61%, eosinos. 4%, lymphos. 29%, monos. 6%).

X-ray chest and I.V.P.: no abnormality.

Treatment.—Diethylcarbamazine (Hetrazan) 100 mg. t.i.d. since 14.10.58.

Comment.—In chyluria, chyle from the intestinal lymphatics is present in the urine. It occurs as a result of obstruction of the thoracic duct or cysterna chyli with consequent back pressure in the lymphatics and gross dilatation of the lymphatic vessels. Subsequently, either spontaneously or as a result of excessive exercise, trauma or mechanical pressure as in pregnancy, rupture of a distended lymphatic vessel into some part of the urinary tract occurs, causing chyluria. The urine is milky white in colour from the fat in the chyle; the degree of whiteness depends on the amount of fat eaten as well as on mechanical factors such as posture or exercise. In our patient, the first morning specimen is whiter than the later specimens. In chyluria, the urine also contains the protein of chyle and microscopically R.B.C.s are usually present, sometimes in large numbers. Sometimes the chyluria clots on standing, from the presence of fibrinogen, but in our patient this has not been noted.

Chyluria must be distinguished from lipuria caused by conditions such as lipæmia in diabetes mellitus, nephrotic syndrome or phosphorus poisoning. In such cases, however, the urine is only slightly turbid due to relatively small quantities of fat only.

Although cases of non-tropical chyluria have been described occasionally from causes such as tuberculous peritonitis, injury of the thoracic duct or neoplasm, the vast majority are due to *Wuchereria bancrofti* (*Filaria bancrofti*). Our patient in his clinical history shows the natural course of the disease, filariasis. Nine years ago, presumably following mosquito bite, he developed lymphangitis of the left forearm when filaria settled in his lymphatics. His attacks of continued fever associated with urticaria, which were labelled typhoid, are likely to have been due to lymphangitis involving the mediastinal and posterior abdominal lymphatic vessels including the thoracic duct and cysterna chyli. Eosinophilia is usually marked at that stage of the disease. Later, owing to recurrent lymphangitis, gradual obstruction of the thoracic duct developed, resulting in lymphangiectases of the distal lymphatics including the lymphatics of the urinary tract. Spontaneous rupture into the urinary tract occurred nine years after the original infection. Similarly, in other cases, obstruction of lymphatics from recurrent lymphangitis can result in elephantiasis of the limbs, or chylous effusions into peritoneum, pleura or tunica vaginalis.

It is likely that adult filariæ are still alive in our patient, since microfilariæ or embryo filariæ were readily found in his blood (Fig. 1). In

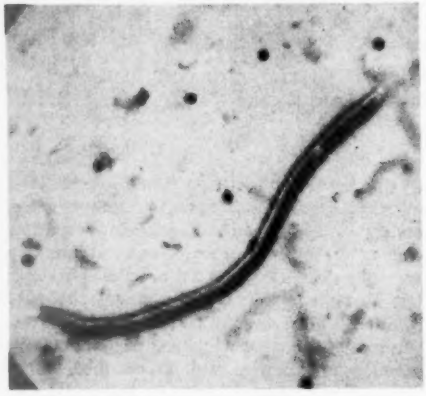

FIG. 1.—×200.

cases of chyluria where microfilariæ are never found, the adult filariæ are presumably dead and possibly calcified, and thus the obstruction of the thoracic duct persists.

Chyluria itself is a relatively uncommon manifestation of filariasis. Ray and Rao (1939), in a personal series of 12,346 cases of clinical filariasis in India, found an incidence of 2%. The clinical course is variable. There is a tendency to remissions, with relapses due to temporary closure and reopening of the fistula. Some, however, are persistent. In the majority of cases little disability results, apart from loss of weight and occasionally anæmia from loss of blood in urine. There are records of patients with chyluria for many years who led a normal life.

No specific therapy is likely to help in chyluria. Diethylcarbamazine (Hetrazan) will kill microfilariæ but it is doubtful whether it has any effect on adult filariæ, and in any case it is unlikely that death of the adult worms will lessen the obstructive symptoms. In our patient, after three and a half weeks' Hetrazan therapy, a few microfilariæ were seen, but all were non-motile and presumably dead. His chyluria is unchanged. Irrigation with silver nitrate solution has been attempted in a few cases and some success claimed where the actual fistulous opening has been located by cystoscopy or pyelography. On the whole, however, advice about cutting down the fat in diet and reassurance as to good prognosis is the most useful line of treatment to prevent the development of neurosis.

POSTSCRIPT.—22.1.59: There has been no chyluria since 3.1.59.

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Dr. W. H. R. Auld: The lipid content of this urine was not constant. Some specimens showed only a faint opalescence, others contained so much fat that cream separated to the top on standing. Fractional analysis (Table I) showed that most of the fat was in the form of neutral triglycerides, with small quantities of cholesterol, minimal amounts of phospholipid, and some free fatty acids. The soaps present were doubtless formed from neutral fat while the specimen was awaiting analysis. These proportions are of the same order as in chyle. When 100 mg. Sudan III dissolved in 40 ml. olive oil was given by mouth together with a light fat-free breakfast, the urine passed four hours later was virtually free of fat and contained no dye. This presumably represented a period during the night when fat absorption from the gut was minimal. Specimens passed at eight hours and later, contained fat and were obviously dyed pink, and traces of dye were still being excreted after twenty-four hours.

It was possible by measuring the urinary fat excretion on a known fat intake to calculate approximately the extent of the chylous leak. On a diet containing 73 grams of fat daily, the urinary fat was about 10 grams/twenty four hours, showing that about 15% of the lymphatic drainage from the gut was being lost through the fistula.

TABLE I.—URINARY FAT EXCRETION

Urine volume	Cholesterol	Phospholipid	Fatty acids		Neutral fat	Total lipid
			Free	As soaps		
Day 1. 1,200 ml.	54 mg./100 ml.	27 mg./100 ml. expressed as lecithin	19 mg./100 ml.	91 mg./100 ml.	419 mg./100 ml.	610 mg./100 ml. 7·3 g./24 hours
Day 2. 1,200 ml.	54 mg./100 ml.	None detected	175 mg./100 ml.	190 mg./100 ml.	621 mg./100 ml.	1,040 mg./100 ml. 12·5 g./24 hours

Total protein: Day 1 = 1·39 g./100 ml. = 15·5 g./24 hr.
Day 2 = 1·50 g./100 ml. = 18 g./24 hr.

Sir Philip Manson-Bahr congratulated Dr. Gottlieb on the manner in which this case of chyluria had been worked out, for very few similar instances of this complication of filariasis were to be found in the literature. Chyluria was historic because the embryo (*Filaria sanguinis-hominis*) was first found in the urine by Demarquay in Paris in 1863 and later, in 1868, by Wucherer in Brazil. The parasite ought still to be known as filaria, as Manson suggested in 1879, when he wished to name his daughter after the adult worm which he had found in an elephantoid scrotum. The evidence was that the obstruction took place in the receptaculum chyli and in the thoracic duct, being caused by dead and cretified adult filariæ. The treatment by Hetrazan generally killed the microfilariæ in the blood, but did not remove the obstructions. Modern opinion was that the addition of injections of Antrypol increased the power of Hetrazan to kill adult filariæ. He hoped that cystoscopy would be done. It might show lymphatic varices round the ureteric orifices which burst, periodically discharging chyle into the urine.

Recurrent Abscesses due to *Necrophorus fusiformis*.—H. ELLIS, M.Ch., F.R.C.S. (for R. O. LEE, F.R.C.S.).

Mr. E. W., now aged 49, was admitted to the Northampton General Hospital in January 1955 with a right loin abscess which required incision on two occasions. Although Gram-negative organisms were seen in films of the pus, no growth was obtained on culture. A persistent sinus followed. Radiographs of spine and pelvis, barium meal and enema and a pyelogram were all negative but showed a fæcolith in the right iliac fossa.

Exploration of the sinus in April 1955 revealed a track into the right iliac fossa. Pain and fever continued and, therefore, appendicectomy was performed in June 1955. The appendix was chronically inflamed, obstructed by a large fæcolith and extended into an abscess cavity in the right loin.

An abscess formed in the right buttock and this was drained in July 1955. In September a left lumbar abscess was drained; on this occasion the organism was identified as *Necrophorus fusiformis*, sensitive to Terramycin. Then destruction of the left femoral head began and Terramycin was commenced. However, abscesses appeared in both femoral triangles and the right buttock, requiring repeated drainage. By the end of 1955 he was well.

In December 1956, after fifteen months' therapy, Terramycin was discontinued; within thirteen days an abscess recurred in the pelvis and right buttock. Terramycin was recommenced and continued for a further twenty-one months until September 1958. A week after stopping the drug a right groin abscess formed, and yielded *Necrophorus fusiformis*. Terramycin has now been started again.

Comment.—The *Necrophorus fusiformis* is an anaerobic, Gram-negative, pleomorphic bacillus. It is responsible for a number of necrotic and gangrenous lesions in animals, for example, calf diphtheria, labial necrosis of rabbits and foot-rot in sheep.

Histologically, the organism produces an intense local inflammatory response followed by necrosis. In humans it is occasionally found to be the responsible organism in puerperal fever, lung abscess and empyema, liver abscess and pyæmia; Alston in 1955 was able to collect 280 cases from the literature of which only 21 were from the British Isles.

The organism is believed to enter the human alimentary tract from animal sources, and lurk there as a saprophyte, only invading if traumata such as tonsillectomy, parturition or appendicitis breach the body's resistance. In the present case, although communication between all the abscess cavities was not actually demonstrated, no doubt direct extension occurred from the original appendix abscess retroperitoneally to both loins, across the pelvis and greater sciatic notch to the right buttock, via the psoas sheaths to both femoral triangles and through the left acetabulum to the hip-joint.

The necrophorus is frequently penicillin-sensitive, although this strain proved resistant. The bacteroides group as a whole is usually sensitive to Terramycin (oxytetracycline) which is the drug of choice in such infections (Garrod, 1955). Because in this case the abscesses recurred both the times we stopped the Terramycin we believe that treatment may have to be continued indefinitely.

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Amyloid Disease following Rheumatoid Arthritis with Advanced Arterial Calcification.—A. M. DENMAN, M.B. (for E. C. WARNER, M.D., F.R.C.P.).

E. W., female, aged 36.

From the age of 18 years this patient has suffered from polyarthritis involving the ankles, knees, wrists and hands, diagnosed at the time as a rheumatoid arthritis. For many years she was treated with physiotherapy and a variety of drugs, but never any vitamin D preparations. Her joints responded poorly to this treatment. When 24, she had symptoms of persistent sinusitis, the maxillary antra were found to contain pus and were subsequently drained. When 33 (in 1955), she developed severe pyoderma which appeared to involve her entire skin surface: after eight months' treatment with cortisone the joints and skin were much improved.

In December 1957 she noticed for the first time a gradual painless swelling of the lower limbs which later spread to the thighs. She began also to experience severe diarrhœa: the urine was found to contain considerable quantities of albumin. These symptoms responded to simple bed rest but in more recent months the œdema of the legs had returned and spread to the abdomen. She also had excessive abdominal distension as well as diarrhœa; on one occasion there was fresh blood in the stool. She was weak and listless and slight effort made her dyspnœic. Her joint pains still persisted. Her weight had fallen by 18 lb. during the preceding year. She had frequency of micturition by day and by night through this period and for eight months had amenorrhœa.

Examination showed a curious slaty complexion, the colour changes of chronic nephritis blending with those of Addison's disease. There was a

little pitting œdema of both ankles, the left knee contained a large effusion and the periarticular tissues were thickened. She had no axillary and scanty pubic hair; the mucous membranes were pale.

Cardiovascular system.—All pulsation was absent in the arteries below the brachial in the upper limb and the femoral in the lower; the more distal vessels were palpably calcified. The blood pressure was 130/70 mm. and had fallen from recordings made in earlier months. The apex beat was not displaced and there were no other abnormalities.

Respiratory system.—The sinuses transilluminated poorly; the lungs were normal.

Alimentary system.—The abdomen was distended. The liver was palpable 7 fingerbreadths below the right costal margin, and was smooth and tender with a resilient rubbery consistency. The spleen tip was just palpable. There was a little free fluid.

Central nervous system.—Normal.

A clinical diagnosis of amyloid disease, affecting the kidneys, liver, spleen, gastro-intestinal tract and adrenal glands was made, secondary to long-standing rheumatoid arthritis and chronic sinusitis.

Investigations.—X-rays of abdomen and limbs show calcification of all major vessels. Fig. 1 shows arthritic changes in right wrist with these calcified vessels. *Blood:* Hb 34%. The anæmia was normochromic and normocytic. E.S.R. 163 mm. in the first hour (Westergren). Transfusion raised the Hb to 81%. *Renal function:* The urine contained protein 10 grams/l. (Esbach): the deposit showed numerous granular and also waxy casts. S.G. fixed at 1010. Blood urea 108 mg.%. Serum calcium 8·3, phosphate 4·5 mg.%. Serum alkali reserve 30 vols. %. *Liver function tests:* Thymol turbidity (1 unit) and Kunkel tests (2 units) normal; serum bilirubin 0·6 mg.%; alkaline phosphatase raised to 26 K.-A. units. Plasma proteins: albumin 3·4, globulin 1·5 grams %, A/G ratio 2·3 : 1·0. *Adrenal function:* 17-ketosteroids less than 1 mg. per twenty-four hours. After ACTH 40 i.u., q.d.s., for three days the figure was only 1·2 mg. per twenty-four hours. Amyloid involvement of the gut was indicated by a flat glucose tolerance curve, the maximum blood sugar being 100 mg.%. Total fæcal fat 29% of dry weight.

Specific tests for amyloid disease.—Four minutes after an injection of Congo red, all the dye had disappeared from the blood and none was recovered in the urine in the subsequent hour. *Gum biopsy* (Fig. 2): Apart from the epithelial cells of the gum, there are numerous capillaries; surrounding the latter are areas of homogeneous hyaline material which stain with Congo red and can only be amyloid tissue. This was confirmed in other sections with crystal violet staining.

On 18.10.58 she was given triamcinolone, 5 mg. q.d.s., but after three days this had to be reduced to 4 mg. per day because of immediate and striking fluid retention: she has gained nearly 2 st. in weight and has gross ascites, bilateral pleural effusions and pitting œdema of the sacral area.

This case illustrates the degree to which calcification of amyloid can occur, even in a young person.

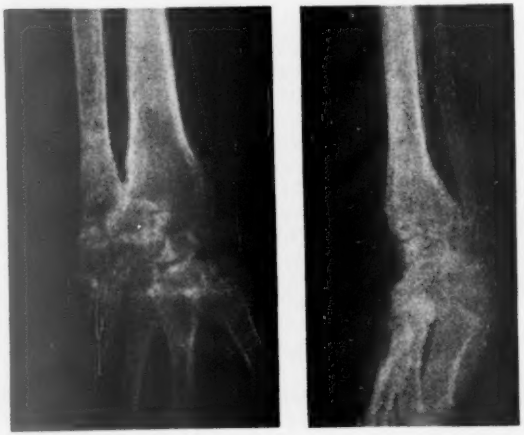

FIG. 1.

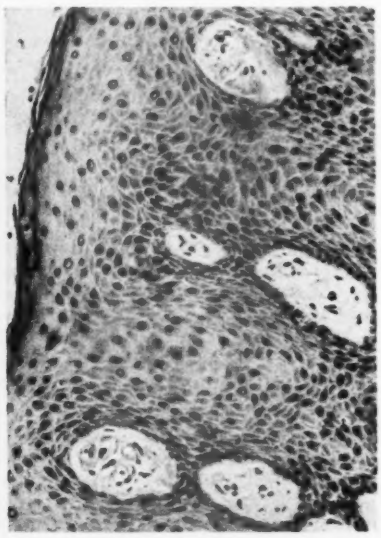

FIG. 2.

Resection of Tracheal Stricture following Tracheotomy, with Primary Anastomosis.—GEOFFREY FLAVELL, F.R.C.S., M.R.C.P.

Most innocent strictures of the trachea previously reported have been due to tuberculosis or laceration. Tracheotomy is now increasingly used in the treatment of severe head injuries, poliomyelitis, "stove-in" chests, myasthenia gravis and a variety of post-operative states in which coughing is ineffective or respiratory mechanics are otherwise impaired. It is life-saving for three reasons:

(1) It enables bronchial secretions to be easily and regularly removed.

(2) It substantially reduces respiratory dead space.

(3) It allows positive pressure respiration to be given with a Beaver respirator via an endotracheal tube with an inflatable cuff.

Two rules must be observed or else the inflatable cuff may provide a third source of tracheal stricture by causing pressure necrosis of the cartilage and mucosa of the trachea because left inflated too long. Rule 1: The cuff should be thought of as being like a tourniquet and deflated for five or ten minutes in every hour. Rule 2: Because red rubber is highly irritant to the mucosa, tubes and cuffs should be made of non-irritating plastics such as polyvinylchloride.

In spite of much experimental work on tracheal reconstruction in dogs very little success has hitherto attended attempts to excise and repair tracheal strictures. Resection with replacement by tracheal homografts or by plastic prostheses is disappointing (Davies *et al.*, 1952; Craig *et al.*, 1953); and experience with reinforced dermal grafts in man when successful has been confined to partial excisions of the wall and the insertion of a patch (Gebauer, 1951), and when more ambitious has failed (Longmire, 1948). Richards and Cohn (1955) attempted excision of a stricture followed by end-to-end anastomosis, but it soon recurred and the patient was left with permanent tracheotomy and tube. They said: "Unfortunately the difficulties of end-to-end anastomosis are great because of scarring and fixation of involved strictures." Mitchel and Davis (1958) had a similar experience. The carinal end of the trachea has been successfully removed when involved by growth (Barclay *et al.*, 1957), the severed main bronchi being reimplanted into it or into each other; but simple strictures are usually well above this level, so that this technique is not applicable to them.

The following case history illustrates some of the difficulties encountered in the management of a simple tracheal stricture, and some technical measures which facilitated repair:

CASE HISTORY

Male, aged 16.

28.9.57: Following road accident admitted unconscious to hospital. Decerebrate rigidity present.

30.9.57: Tracheotomy performed and Jame's cuff tube inserted. Hypothermia under gas and oxygen anæsthesia maintained for five days.

26.10.57: Regained consciousness. Right hemiplegia. Cough reflex present, so tracheotomy tube removed.

10.11.57: Evidence of increasing tracheal obstruction. Bronchoscopy revealed granulating stricture of the trachea about 20 cm. from upper incisors. It was dilated, and two days later the patient was transferred to the Department of Thoracic Surgery at the London Hospital. At this time he was disorientated and cyanosed. The tracheotomy wound was healed and bilateral bronchopneumonia due to sputum retention was diagnosed. Bronchoscopy, dilatation of the stricture and aspiration of much purulent sputum caused transient improvement but the stricture soon recurred, so the tracheotomy was reopened on 14.12.57. The stricture was once more dilated and a Portex (plastic) tube passed through it.

For the next nine months nothing more was done. Though the mucosa looked normal at bronchoscopy, whenever the tube was removed a rigid, tight stricture developed again within five days, nearly causing death by strangulation. However, recovery from the head injury progressed well, and it was hoped that the tracheal wall might become rigid again in time. The sputum was—and continued to be—heavily infected with staphylococci insensitive to penicillin, streptomycin, Terramycin and Chloromycetin. No improvement followed the passage of time, so at last a radical excision of the stricture was decided upon.

Operation (10.9.58).—A right thoracotomy was performed through the fourth intercostal space with the patient face-down on the operating table. The anæsthetic (Dr. D. Stride) was given through a left endobronchial tube.

After division of the azygos vein, the trachea was found to be fixed in the mediastinum by dense scar tissue and had to be freed by sharp dissection throughout its whole intrathoracic length. This dissection included the origins of both main bronchi, so that a tape could be passed round the carina (Figs. 1 and 2). The right inferior pulmonary ligament was divided to

increase the mobility of the right lung. The site of the stricture (surprisingly) could not be felt or seen, so a longitudinal incision had to be made in the middle of the membranous posterior tracheal wall in order to find it. It was located just below the thoracic outlet. The whole circumference of the trachea in which it lay, just over 2 cm. in length, was then excised and the longitudinal wound closed. Interrupted sutures of No. 90 linen thread were placed, but not tied, round the circumference of the trachea. Traction on the carinal tape now approximated the cut ends so that all the sutures could be tied without tension, and end-to-end anastomosis (round the anæsthetist's endobronchial tube) was accomplished (Fig. 2). The chest was then closed, two apical, water-sealed drainage tubes being left in the right pleural cavity.

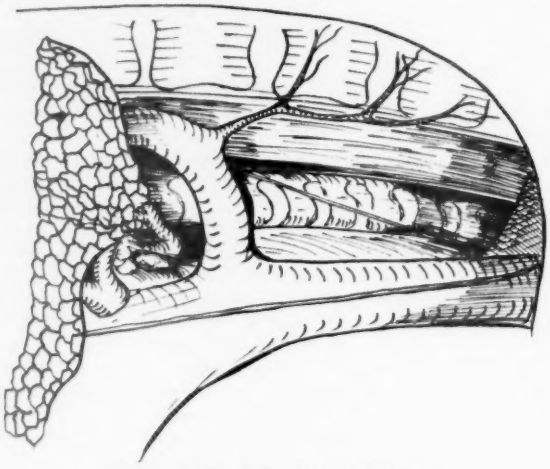

FIG. 1.—View of superior mediastinum.

Post-operatively suction was applied to these tubes, and the patient was nursed head-down for the first ten days in order to diminish traction until the anastomosis was thought to be healed. The tracheotomy was maintained for three weeks.

Recovery was uneventful and complete, the patient was discharged on 7.10.58, by which time bronchoscopy showed no evidence of stricture, and the tracheotomy had healed. Subsequent tomography of the trachea (Fig. 3) shows a shallow lip at the point of anastomosis, but no stricture. The patient has returned to work.

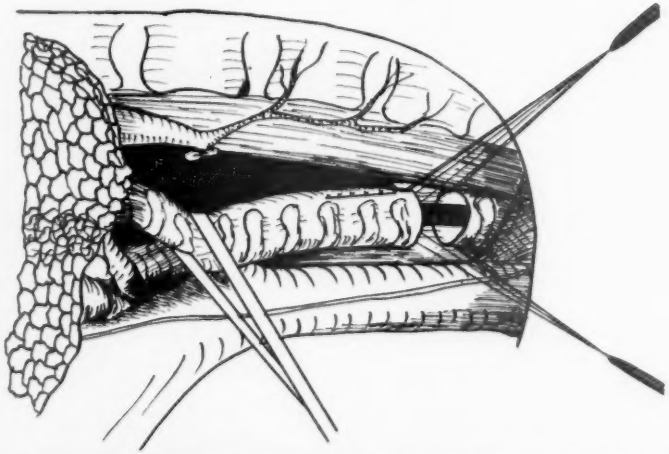

FIG. 2.—The trachea has been mobilized from the mediastinum, tapes having been passed round the carina to afford upward traction. The stricture has been excised and the anastomosis begun round the anæsthetic tube.

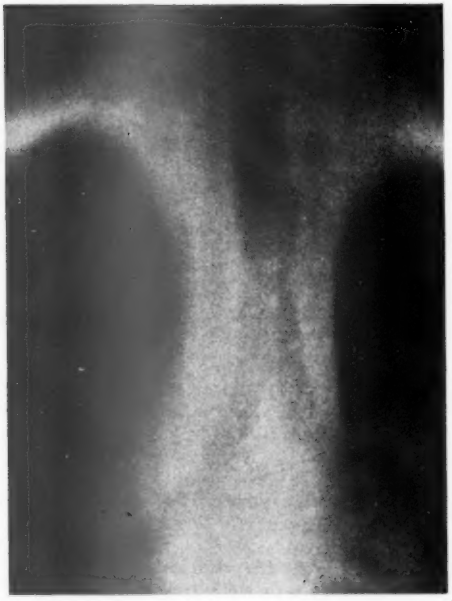

FIG. 3.—Recent tomogram of the trachea shows a slight lip at the site of anastomosis. No stricture.

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Pulmonary Aspergillosis.—A. R. TANSER, M.B. (for RICHARD ASHER, M.D., F.R.C.P.).

H. L., aged 59 years. Recurrent bronchitis since 1948.

October 7, 1957: Admitted to the Central Middlesex Hospital with acute bronchitis, febrile in spite of antibiotic treatment.

October 29, 1957: Transferred to Pinewood Hospital: feverish, wheezing and dyspnœic with signs of consolidation at the right base. X-rays taken during the next two months showed progressive consolidation in the left lung and patchy consolidation in the right (Fig. 1). Cavitation was shown in the apex of the left lower lobe, and in the left upper lobe and lingula. There was no response to antibiotics.

The sputum grew *H. influenzæ*, *B. proteus* and, on many occasions, *Aspergillus fumigatus*. No tubercle bacilli were found at any time.

At bronchoscopy, only acute inflammatory changes were seen.

W.B.C.(17.12.57): 13,200/c.mm. with 4% eosinophils.

January 1958: Clinical and radiological resolution occurred leaving bronchiectasis, especially in the left upper zone.

March 1958: Tomograms showed that a mycetoma had developed in a bronchiectatic cavity at the left apex. Inhalations of brilliant green were ineffective and were stopped because they provoked hæmoptysis.

April 2, 1958: Discharged from Pinewood. Re-admitted to the Central Middlesex Hospital on 3.5.58 with hæmoptysis, wheezing and dyspnœa. These responded to treatment and he was discharged after ten days.

July 27, 1958: Again admitted with hæmoptysis. *Aspergillus fumigatus* still present in the sputum. The hæmoptysis persisted until October 13, 1958.

October 13, 1958: A wedge resection of the left apex was performed (Mr. R. Laird). The specimen showed a mycetoma lying in a cavity 1·5 cm. in diameter (Fig. 2).

Comment.—Aspergillus fumigatus is a fungus commonly found in vegetable dusts but there is no history of such exposure in this case.

Gross consolidation, failing to respond to antibiotics and associated with wheezing and residual bronchiectasis, suggests the "allergic aspergillosis" described by Hinson *et al.* (1952) except that here the eosinophil count was less than 1,000/c.mm.

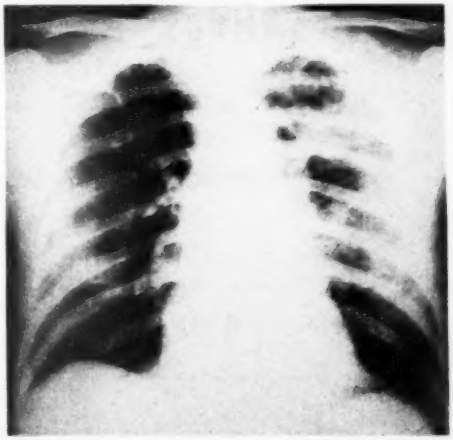

FIG. 1.—Chest X-ray taken on 4.12.57, showing consolidation especially in the left lung.

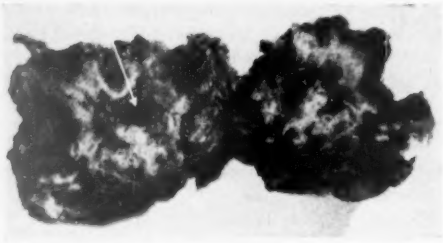

FIG. 2.—Operation specimen opened. The mycetoma is on the left (arrowed).

A mycetoma is a mass of fungus mycelium and blood products, growing as a saprophyte in an existing cavity, usually bronchiectatic, tuberculous or neoplastic.

In this case, it is possible that the cavity in which the mycetoma formed was caused by the *Aspergillus fumigatus* itself during the "allergic aspergillosis".

Acknowledgments.—I would like to thank Mr. A. Booker for the photographs, and Dr. J. J. McCann and Mr. R. Laird for permission to publish this case.

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The following cases were also shown:

Unilateral Proptosis from a Cavernous Orbital Hæmangioma.—Mr. H. E. HOBBS.

Argentaffinoma with Hepatic Metastases.—Dr. H. WYKEHAM BALME and Dr. R. R. DE MOWBRAY.

Enterogenous Cyst of the Œsophagus.—Miss MURIEL C. WATERFALL.

Keratoconjunctivitis Sicca with Hepatosplenomegaly, Pancytopenia and Hyperglobulinæmia.—Dr. E. M. SPENCE (for Dr. NIGEL COMPSTON).

Mitral Stenosis without Diastolic Murmur.—Dr. I. E. EVANS (for Dr. RALPH KAUNTZE).

Rheumatoid Arthritis with Extensive Nodular Formation.—Dr. C. TOH (for Dr. K. P. BALL).

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BOOK REVIEWS

Cancer. Ed.: Ronald W. Raven, O.B.E.(Mil.), T.D., F.R.C.S. Vol. 4. (Pp. ix+532+23; illustrated. 85s.) London: Butterworth & Co. (Publishers) Ltd. 1958.

This volume deals with the clinical aspect of malignant tumours including the principles of their treatment. Apart from the first chapter on the staging of cancer by Harmer, who is well known for his enthusiasm for this subject, the contributions are mainly according to regions. With three exceptions, the authors are all surgeons. The editor contributes the chapters on the oropharynx, œsophagus, and breast, and among others well known for their contributions to their subject are Aylett on the colon, Barrett on the lung, Fergusson on the prostate, Pennybacker on the nervous system, and Tanner on the stomach. The international character of this volume is less marked than that of previous volumes, and the editor has only found it necessary to call in from the United States Dr. Pack, who contributes the chapter on the liver and biliary passages, and, with his colleague Dr. Ariel, that on sarcoma of soft tissues. The volume as a whole well represents current views.

Emergency Treatment and Management. By Thos. Flint, Jr., M.D. 2nd ed. (Pp. xvii+539; 56s.) Philadelphia and London: W. B. Saunders Company. 1958.

This book is designed to give to the practitioner the information he will require to enable him to deal with emergencies in his practice. The author has stuck closely to his purpose, an instance of this being his wide advice against giving corticotrophin in status asthmaticus until the patient is admitted to hospital.

An example of some of the practical points with which his book is filled is the recommendation that no patient suspected of having a coronary thrombosis should be allowed to go to hospital in a private car, as the crew of an ambulance would ensure a patient against all effort.

A large amount of the book is devoted to the treatment of poisoning by many and various agents, and there is a useful section on toxic reactions to drugs in therapeutic doses. The portion devoted to toxic ingredients is less valuable to British than to American readers as naturally a number of the preparations are proprietary ones and unknown in this country.

The treatment of fractures and boils is described along simple lines, and the whole book should be useful to practitioners and has the advantage of being sufficiently small to be slipped into a reasonably sized bag.

Comparative Anatomy and Physiology of the Nose and Paranasal Sinuses. By Sir Victor Negus, Hon.D.Sc.(Manchester), M.S. (London), F.R.C.S.(Eng.), Hon. F.R.C.S. (Edin.), Hon. F.R.C.S.(Ireland). (Pp. xv+402; illustrated. 70s.) Edinburgh and London: E. & S. Livingstone, Ltd. 1958.

Sir Victor Negus produced his monumental work on the mechanism of the larynx almost thirty years ago and in its preparation he examined examples of every branch of animal life. From these widely divergent members of the animal kingdom he traced the development of the larynx from its most primitive form to the highly specialized structure found in man and other species.

In the preparation of the present volume a veritable Noah's Ark of species has been collected, dissected and analysed. The functions of the nasal and the accessory cavities have been considered in relation to their anatomical structure and to the mode of life and the requirements of the animal concerned. It has been shown how the structure of the nose varies according to whether its owner lives in the treetops, in the sea or on the ground, and whether his normal environment is arctic, tropical, or temperate. It also depends on whether he is carnivorous or herbivorous in whole or in part, and whether smell plays a major or a minor part in ensuring his survival. Considerable sections describe the mechanism of olfaction, and also that of conditioning of inspired air and show how the habitat and the habits of the animal may modify these mechanisms.

The volume is copiously illustrated—with imaginative drawings, with simple diagrams, with X-ray photographs and with electron-micrographs, with more ordinary light photomicrographs of histological preparations and with photographs and reconstructions of the author's dissections of every kind of nose. There is a glossary of the genera and species investigated, and chapters describing, in its various aspects, the nose of man. Sir Victor was reluctant to bestow unchallenged pre-eminence on man on account of the high state of development of his larynx, and he relegates him

to a very lowly position on the strength—or the weakness—of his degenerate nasal apparatus.

The touch of cynicism on the part of the author in his final three paragraphs appeals to the reviewer and had these words been printed just a hundred years ago, they would have added fuel to the fires of controversy which followed the publication of the "Origin of Species"—to which this book is a logical and very worthy sequel.

De Circulatione Sanguinis. The Circulation of the Blood. Two anatomical essays by William Harvey together with nine letters written by him. Translated by Kenneth J. Franklin. (Pp. xxiii+184; illustrated. 22s. 6d.) Oxford: Blackwell Scientific Publications. 1958.

All who possess Professor Franklin's admirable translation of William Harvey's *De Motu Cordis* will want to acquire this companion volume *De Circulatione Sanguinis* which contains two essays written to Jean Riolan junior and nine letters to other distinguished men. In the letter to Schlegel there is described a valuable additional experiment to prove the circulation through the lungs. In several places there are interesting autobiographical comments. It is significant of Harvey's intelligence that in a letter written only two months before his death in which he admits that he was not only ripe in years but also "a little weary", he still throws out the stimulating suggestion that there is no "surer route to the proper practice of medicine than if someone gives his mind over to discerning the customary law of Nature through the careful investigation of diseases that are of rare occurrence". There is no sign of ageing in that advice.

Urology in Outline. By T. L. Chapman, Ch.M., F.R.C.S.(Eng.), F.R.F.P.S.(Glas.). (Pp. vii +176; illustrated. 27s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1959.

Mr. T. L. Chapman has written a book of some originality on urology. In it there are no pictures of X-ray films, and no other illustrations apart from a large number of drawings and diagrams.

These figure at the end of each chapter, and should be of the greatest value to the medical student in explanation of the text. Most of them are simple line drawings which can be easily memorized.

The author has wisely not taken sides on subjects when the views are conflicting. He has skated over the pathology of the urinary tract, but in his preface he is careful enough to state that "it is hoped that this modest volume will be helpful to those who would like to acquire quickly an elementary knowledge of this subject."

This little book will most certainly be of considerable assistance to the student in the early years of his training, but he will need for advanced study to read one which provides more information than is available in "Urology in Outline".

The publishers have borne in mind the financial position of those who may purchase Mr. Chapman's book, and so the price at 27s. 6d. is reasonable.

Hemophilic Arthropathies. By Henry H. Jordan, M.D. (Pp. xv+255; illustrated. 63s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

Dr. Jordan's remarkable experience has been gained as Chief of the Hemophilia Clinic at the Lenox Hill Hospital, New York, a clinic originally sponsored by the National Hemophilia Foundation which is doing so much for the welfare of "bleeders" throughout the United States. The book aims at providing details of the orthopædic care of these patients, the correction of their deformities, and the protection of joints from further hæmorrhages. More than half of the book is made up by case histories of the 56 patients reviewed; from these many tables of statistics are drawn up which are of little value, but the details given of the art of straightening contractures and of the subsequent brace-making required could scarcely be bettered. No attempt is made to discuss hæmatological aspects, nor is any reference made to the different types of the disease; this is essentially a monograph by an orthopædic surgeon written for his colleagues in orthopædics, and as such is a valuable guide in this difficult subject.

Preventive Medicine and Public Health. An Introduction for Students and Practitioners. By Fred Grundy, M.D., M.R.C.P., D.P.H. 3rd ed. (Pp. vii+309; illustrated. 25s.) London: H. K. Lewis & Co., Ltd. 1957.

Earlier editions of this book are already well known and appreciated both by medical students and by teachers of preventive medicine. Minor changes only have been made in the text, aimed mainly at bringing it up to date, but an appendix has been added giving useful suggestions for further reading. The book has the distinction of being one of very few written at exactly the right level for the medical student. This is achieved by the clear exposition of carefully selected material, and not by any compromise with the facts. Thus it is also useful to more advanced students, who want an accurate summary of the

essential features of public health practice in this country. It is most readable and attractively presented, though the style is rather impersonal and glare from excessively shiny paper is sometimes troublesome. There is little unnecessary detail, except perhaps on the Midwives' Acts, and the book would be sufficiently comprehensive for students' needs but for the deliberate omission of information on occupational health. If the author could be persuaded to overcome his modesty and include a chapter on this subject in the next edition, its value would be increased.

The subject order is somewhat unusual in that practice precedes theory and principle, and history is the last aspect to be dealt with. The emphasis throughout is on public health practice, particularly from the point of view of the medical officer of health. Local authority health services are well described but the extent to which modifications may be needed to meet changing problems is not considered. The place of the general practitioner in preventive medicine also deserves more space. Chapters describing statistical methods and trends of mortality and morbidity are first class, and better than those in several much larger books; those on heredity and population growth are also very good, but other aspects of epidemiology are in general less well covered. Such minor imperfections do not seriously detract from the excellence of this introduction to preventive medicine and public health for medical students.

Modern Trends in Surgical Materials. Ed.: Leon Gillis, M.B.E., M.Ch.Orth., F.R.C.S.Eng., F.R.C.S.Edin., D.L.O. (Pp. xi+266+9; illustrated. 72s. 6d.) London: Butterworth & Co. (Publishers) Ltd. 1958.

Human tissues had only catgut with which to contend a few years ago. To-day a bewildering variety of substances and ligature materials are introduced into surgical wounds and it is imperative for the surgeon to know something of their physical and chemical properties and the pathological responses which they elicit.

This book sets out to supply such information to the busy practising surgeon. The first third or so of the book mainly concerns the use of metals by orthopædic surgeons. The changes occurring in metal and bone after implantation and the pathological effects from such materials are all described very clearly. In similar fashion the plastic materials available are also reviewed.

Chapters then follow describing the use of various materials in dental, plastic, thoracic and neurosurgery. The place of arterial homografts and plastic prostheses in vascular surgery is reviewed and guidance is given about the preparation and storing of arterial homografts. A chapter on the preservation of tissues in general for surgery is followed by an interesting description of the manufacture of artificial limbs and there is a useful summary of methods of sterilization.

There is something in this book for every surgeon and it would appear to be of particular value to orthopædic surgeons.

Differentialdiagnose innerer Krankheiten. By Prof. Dr. Robert Hegglin. 6th ed. (Pp. xvi+819; illustrated. DM. 79.50.) Stuttgart: Georg Thieme Verlag. 1959.

The great success of this finely produced Swiss monograph on the Continent is attested by the fact that it has already passed through six German editions and four Italian and Spanish translations since its first appearance seven years ago.

The text is arranged in twenty-five chapters, each entitled with the name of some important symptom or sign. Each particular chapter theme, after an appropriate short general introduction, is then expanded along some clearly outlined system of classification to take up *seriatim* the possible circumstances under which it may be encountered clinically. The author makes no attempt to provide a simplified guide to diagnosis, but he does furnish admirable discussions of relevant modern knowledge which cannot fail to be helpful to the practising physician confronted with an obscure case. And quite aside from such an immediate purpose, it would also give him many hours of pleasant and profitable browsing.

The German text is set out in a simple, direct and consecutive style, and follows current international usages for its technical terms. Each chapter is followed by a short list of appropriate modern references; most of them are German and Swiss articles, but there is a fair sprinkling of American, British and French ones as well. The book contains over 500 beautifully produced illustrations, many in colour. Its format is excellent and its binding satisfactory.

The Bacteriology of Tuberculosis. By Egons Darzins, M.D. (Pp. xi+488; illustrated. 80s.) Minnesota University Press. London: Oxford University Press. 1958.

Despite all the recent progress in the control and prevention of tuberculosis, the tubercle bacillus still presents many unsolved problems. The author has dealt with these in five main sections devoted to morphology, growth, diagnosis, pathogenicity and experimental pathology. Part I (Morphology and Cytology of the Tubercle Bacillus) covers physical, biological and chemical methods in identifying cell structures. Part II (Sources of Energy and Growth of the Tubercle

Bacillus) discusses the metabolic activities of the organisms in nutrient and non-nutrient media, the sources of carbon, nitrogen and phosphorus, mineral requirements and growth factors. Part III is devoted mainly to diagnostic bacteriology and discusses the many methods available for isolating tubercle bacilli from pathological material. In Part IV the types and pathogenicity of tubercle bacilli are discussed, while Part V deals mainly with tuberculosis in experimental animals, though there is a final chapter (the thirtieth in the book) on hazards and precautions in the laboratory.

This book is full of important facts about the tubercle bacillus presented with a deliberate emphasis on the historical approach, but also with attention to the latest developments. Original authors are constantly referred to in the text, there are excellent illustrations and there is a full list of references, and an author and subject index. In the list of references (called Bibliography) journals appear not by name but by number. The name of a journal has to be found by reference to a separate list. This method, though it has obvious drawbacks, does save space—and the author has wisely decided to give full titles in the references even at the cost of much extra space.

This book has a few minor defects—the style is not always quite idiomatic and at times there are rather lengthy excursions into discussions of techniques and methods which are not strictly relevant. But the book has filled a gap adequately and will be found useful and informative by workers interested in many different aspects of tuberculosis.

Difficult Diagnosis. A Guide to the Interpretation of Obscure Illness. By H. J. Roberts, M.D. (Pp. xi+913; illustrated. £6 13s.) Philadelphia and London: W. B. Saunders Co. 1958.

All of us enjoy talking of our difficult cases and many like to browse through books that relate those of others in the form of medical bedside reading. Dr. Roberts has resisted the temptation to do this and has skilfully synthetized a mass of facts into a readable narrative from which information can be readily extracted. This he has achieved in part by good arrangement, classification and cross-referencing, together with careful heading and sub-heading, but in the main it has been done by sticking to the assumption that a reasonable amount of factual knowledge will already be possessed by the readers, thus enabling the highlights to be accentuated and special points to be made.

The chapter on iatrogenic illness serves as an example. It begins with a well-arranged list of conditions cross-referenced to the text, and then a number of states are further discussed, some in a few lines which are sufficient to make the main points, others, such as radiation sequelæ, requiring several pages of most interesting reading.

The book is divided into two parts. The first is clinical and the second deals with the assessment and place of investigations in diagnosis. Here the value of the test is discussed, and practical matters relevant to its use are brought out without reference to technical details.

The illustrations are collected together in the form of an atlas, which is a useful arrangement as it enables reference to a single plate to be made at several points in the text. The pictures themselves are clear and well chosen, few seeming to be redundant, and the reproduction is of high quality.

The references, which have been selected with great care, contain papers published as late as October 1957, and thus are as up to date as could possibly be expected.

An enormous amount of trouble has been taken with this book, not only to inform the reader but also to help him to use and enjoy it, and it is certain that many physicians will feel grateful to the author and look forward to further editions. The chief source of wonder is, however, that one man has been able to find time to amass so much information and to write it down in an acceptable form.

Pathology for Students of Dentistry. By George L. Montgomery, T.D., M.D., Ph.D., F.R.S.E., F.R.F.P.S. (G.), F.R.C.P.E. 2nd ed. (Pp. vii +307; illustrated. 40s.) Edinburgh and London: E. & S. Livingstone, Ltd. 1958.

This book has attained the dignity of a second edition in a period of five years, a sure indication of its popularity and usefulness. It is indeed an extremely competent textbook written on more or less conventional and well-tested lines. It is well and generously illustrated, in a number of instances in colour of good quality. Limitations of the size of the book have to be taken into account but it is necessary to say that the opportunity seems to a large extent to have been missed to relate "pathology" to the basic biological training students will have received in preparation for a study of this subject. In this connexion emphasis might have very usefully been laid on the fact that the border between "pathology" and physiology is blurred or even non-existent and that much of pathology concerns the disturbance of normal function by the processes of disease.

The principal change that has been made in the second edition is the replacement of a number of illustrations by others either of better quality or more instructive.

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